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PHEOCHROMOCYTOMAS AS CAUSE OF UNEXPECTED OPERATING ROOM DEATHS*

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The induction of anesthesia and the performance of surgery carry with them a certain calculable risk. Nevertheless, it is disturbing to all concerned when an apparently good-risk patient suddenly goes bad and dies. These unexpected deaths are usually thought to be caused by cardiac arrest or by hemorrhage. During the last seven years we have encountered two instances of unexpected operating room deaths that were due to a different cause. The usual emergency measures did not suffice and a specific form of drug therapy would undoubtedly have been preferable.

CASE REPORTS

Case 1. Mrs. I. H. S., age 52, was hospitalized September 15, 1953, with menorrhagia and a sensation of heaviness in the lower abdomen due to a large uterine fibroid. A preoperative checkup by an internist revealed no evidence of increased operative risk and her blood pressure was 140/90. She was taken to surgery on the day after admission. Anesthesia was induced by intravenous Pentothal followed by cyclopropane in a semiclosed system. Preinduction blood pressure was 160/100 and the pulse was 120 per minute, but soon afterward the blood pressure rose to 180/100 and the pulse slowed to 76. During the next 30 min. the blood pressure gradually rose to 210/150. By the time the peritoneum was opened her pulse suddenly rose to 190 per min. and became somewhat irregular. Surgery was stopped and the cyclopropane discontinued. Atropine, 0.5 mg., was given intravenously and a cardiologist

(K. A. C.) was called. All anesthetic agents were discontinued and straight oxygen administered. Despite this she showed slight cyanosis and moist rales were evident over both lung fields. An electrocardiogram showed supraventricular tachycardia with left axis deviation and slight ST segment depression, which was thought to be due to the rapid heart rate.

Suspecting that the blood pressure and pulse response to anesthetic might be due to excessive circulating pressor amines, the surgeon was asked to palpate the adrenal glands for a possible tumor. This was done through the open incision and none was evident. Because of this, benzodioxane hydrochloride (adrenolytic agent) administration was discontinued and the patient's pulmonary congestion treated intravenously (i.v.) with Pronestyl (500 mg.) and ouabain (0.5 mg.). This had little effect on the heart rate and her condition worsened. Aminophylline, which was given for bronchial spasm, and Pronestyl (200 mg.) were both ineffective. The patient developed ventricular fibrillation and died 2 hours after starting anesthesia (fig. 1). At autopsy a large adrenal tumor measuring 10 by 9.5 by 8 cm. was found, which had practically replaced the left adrenal gland and was depressing the adjacent kidney. On cut section it showed a spongy yellow appearance. Microscopically the tumor showed considerable pleomorphism and some degenerative changes. In general, the cells were large with a poorly outlined granular cytoplasm which showed chromate granules. There was no evidence of malignancy. These findings are typical for a pheochromocytoma (fig. 2).

Case 2. Mrs. F. H., age 66, was hospitalized on September 14, 1959, for a vaginal hysterectomy and repair of a cystocele and rectocele. Anesthesia was induced with Pentothal and followed with cyclopropane in a semiclosed system. Her preinduction blood pressure was 140/90 with a pulse

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of 95 per min. The next blood pressure reading, 15 min. after starting the anesthetic, was 195/95 with a pulse of 98. Shortly afterward the blood pressure fell to 140/90 whereas the pulse suddenly increased to 160 to 170 per minute. When cyanosis appeared the anesthesiologist became concerned and appraised the surgeon of the fact that things weren't going too well, and he suspected the patient might have had a myocardial infarction. A cardiologist (K. A. C.) was called to see the patient for the first time. Examination revealed rales over both lung fields, cyanosis and a marked tachycardia. An electrocardiogram showed supraventricular tachycardia with left axis deviation,

a horizontal heart and ST segment and T wave changes probably due to the rapid rate. A presumptive diagnosis of shock due to a pheochromocytoma was made and, in spite of a blood pressure of near normal, 5 mg. of regitine (adrenolytic agent) were given i.v. without notable effect. Because pulmonary congestion was rapidly increasing, she was given ouabain, 0.5 mg. i.v., and 30 min. later 0.4 mg. of Crystodigin was given. These drugs had little effect on the pulse and pulmonary congestion, so another 0.25 mg. of ouabain was given. Surgery was hastily completed and the patient transferred to the recovery room in a precarious condition with a blood pressure of

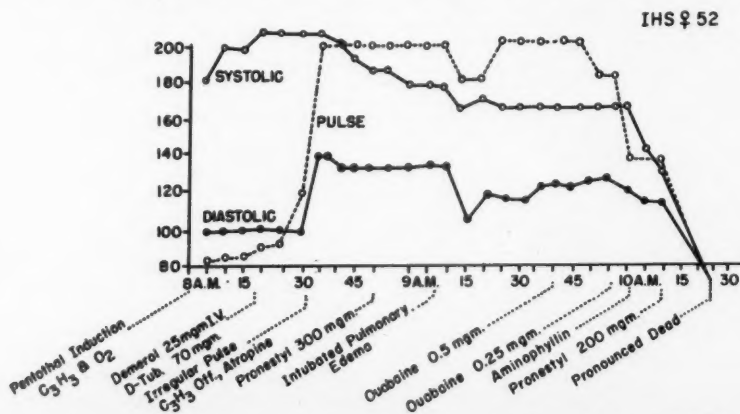


FIG. 1 (case 1). Chart of blood pressure and pulse from induction of anesthesia until death. The medications given to the patient are also recorded.

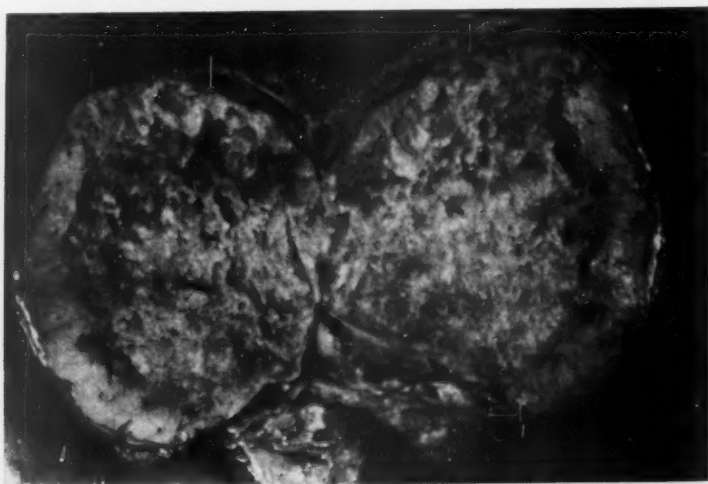


FIG. 2 (case 1). Tumor found at autopsy in left adrenal gland. It measured 10 by 9.5 by 8 cm.

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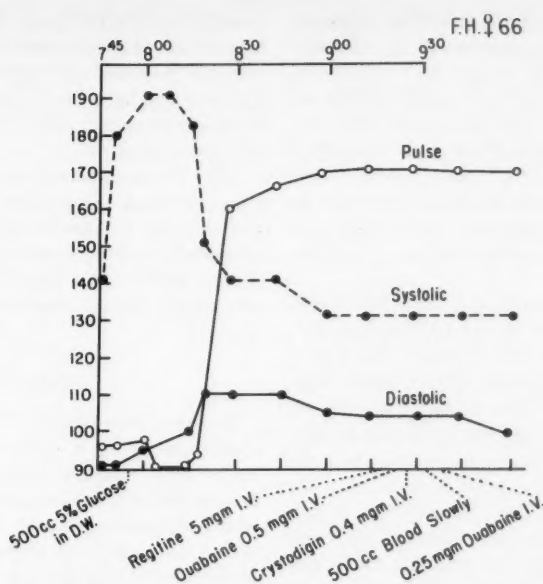


Fig. 3 (case 2). Chart of blood pressure and pulse from induction of anesthesia until death. Also, the medications given to the patient are recorded.

130/100 and a pulse rate of 170 (fig. 3). She gradually awakened and responded. This situation persisted until she suddenly became very cyanotic, pulseless and died 6 hours after the beginning of the anesthetic.

At autopsy the striking findings were in the right adrenal gland where we found an ovoid tumor which measured 4.3 by 4 by 3.5 cm. and weighed 23 gm. The tumor was eccentrically located and had a considerable amount of normal gland around it. The cut surface was pinkish gray in color with areas of cystic changes and softening. The opposite adrenal gland weighed 6 gm. Microscopic section of the right adrenal showed a typical pheochromocytoma surrounded by a small amount of semiatrophic adrenal tissue.

DISCUSSION

Pheochromocytomas arise from the medullary portion of the adrenal glands. They are usually benign (90 per cent) but occasionally are malignant (10 per cent). They occur more frequently on the right side than on the left, or they may be bilateral. They may produce so few symptoms that they frequently go unrecognized, but in a typical case will produce episodes of hypertension, sweating, headache, and even hemorrhage. These symptoms are frequently initiated by

heavy lifting, straining or stopping. If the lesion is suspected, and the patient is hypertensive at the time, adrenolytic agents as phentolamine (Regitine) and benzodioxane will promptly reduce the pressure to normal and relieve the patient of the other symptoms. On the other hand, if the patient is normotensive, an attack can be induced by the injection of 0.05 mg. of histamine base intravenously and then the resulting hypertension controlled by injecting either phentolamine (Regitine) or benzodioxane. When these tests are positive then one should determine the catechol amines excreted in a 24-hour urine specimen. If this is markedly elevated then the diagnosis is quite certain.

X-rays following a retroperitoneal air injection via the perirectal route will help to locate the site of the lesion.

During the past seven years we have had the good fortune of caring for six patients with pheochromocytomas and following them through to the successful surgical removal of their tumors. On induction of anesthesia each patient invariably had a hypertensive episode which was readily controlled by rapid intravenous administration of adequate adrenergic blocking agent (benzodioxane or phentolamine (Regitine)). None

of the patients developed the severe hypertension, tachycardia or shock experienced by the two patients here described. All six made uneventful recoveries and have remained well since removal of their tumors. They did not receive cyclopropane, all being anesthetized with Pentothal, ether and nitrous oxide. Cyclopropane in the presence of epinephrine sensitizes the heart to ventricular arrhythmias and not infrequently results in ventricular tachycardia and/or fibrillation.

It is estimated that between 700 to 800 deaths occur each year from pheochromocytomas and, of the people that are alive and have this pathology, only about 40 per cent of them will be diagnosed before death.² Even though the incidence of these tumors in the general population is small, surgeons and anesthesiologists may unexpectedly encounter them. Both should be mindful of the possible presence of these tumors and include in their history taking such questions as might lead to their suspicion, especially in the hypertensive cases. Where there is suspicion the appropriate adrenolytic drug should be administered or provocative tests performed. If these are positive then retroperitoneal air studies should be done. If these studies confirm the diagnosis, then surgical removal of the tumor should be done prior to any elective surgery.

In cases with hypertension, cyclopropane is probably not the anesthetic agent of choice. If a normotensive patient becomes hypertensive or if a hypertensive case develops extreme tachycardia with induction of anesthesia, then the cyclopropane should be stopped and ether with oxygen in closed system used. Adrenolytic drugs, preferably phentolamine (Regitine) should be started at once in adequate doses to restore normal blood pressure and to slow the pulse. This may require as much as 40 to 50 mg. Surgery should be stopped or concluded as rapidly as possible. Once the patient has developed marked tachycardia and shock, the chance of salvaging him is not good. Some patients develop a mild hypertension on induction of anesthesia which quickly subsides as anesthesia progresses. As far as can be determined there would be no harm in administering phentolamine (Regitine) to a patient who develops hypertension during induction of anesthesia, even though his hypertension is not due to excessive circulating Adrenalin. Usually the

blood pressure elevation is of a greater magnitude in cases of pheochromocytomas and as it rises the pulse becomes quite slow, whereas with the excitement of induction in the normal individual, the blood pressure increase is accompanied by an increase in heart rate.

After the unsuspected case of pheochromocytoma develops tachycardia, pulmonary edema and shock, it is doubtful whether large doses of adrenergic blocking agents will help. The patient should, however, be digitalized rapidly and the pulmonary edema combated in every way possible.

SUMMARY

We have presented two cases of unsuspected pheochromocytomas. Upon induction of anesthesia these patients developed marked hypertension with a bradycardia and later tachycardia which ultimately resulted in shock, pulmonary edema and death. At present only about 40 to 50 per cent of the patients with pheochromocytomas have sufficient symptoms to be diagnosed, so some of them, unfortunately, will receive anesthetics for other procedures and get into serious trouble. We urge that all physicians responsible for checking the patients preoperatively be aware of this danger and make a special effort to detect and correct the condition before undergoing elective surgery. When the condition is first suspected or detected after anesthesia is started, then early and adequate use of adrenolytic agents (Regitine) should be started at once. It may require as much as 50 mg. to control the hypertension. When its usage is delayed only a few minutes the results are extremely poor. Apparently no harm will result if Regitine is used on a patient with hypertension from other causes.

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REGIONAL PERFUSION FOR CANCER*

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The technique of regional perfusion, as suggested by Klopp and co-workers^{2,3} and developed by Creech and co-workers,¹ was instituted at The University of Texas M. D. Anderson Hospital and Tumor Institute in December 1957, for the study and treatment of patients with cancer. Thus far, 160 perfusions have been performed for 128 patients. The majority of the perfusions have been for malignant tumors of the extremities, chiefly melanomas, a considerable number for pelvic cancers, and several for cancers of the head and neck. The number of different drugs employed has been limited in an effort to obtain meaningful data on their effects. With few exceptions, nitrogen mustard and phenylalanine mustard have been chosen.

MATERIALS AND METHODS

The equipment for this procedure consists of two Sigmamotor pumps and a small, disposable bubble oxygenator.† The latter is primed with 500 ml. of heparinized blood, and a mixture of 95 per cent oxygen and 5 per cent CO₂ is delivered at the rate of 3 to 5 L. per min. Heparin is administered systemically *via* the intravenous route, in a dose of 2 mg. per kg. of body weight (100 U.S.P. units per mg.). As a rule, the patient is given a vasodilating agent (papaverine, 180 to 300 mg.) before the introduction of the chemotherapeutic drug. Nitrogen mustard is administered in divided doses of 10 mg. each, and perfusion is continued approximately 20 minutes after the last injection. If phenylalanine mustard is to be employed, 3 to 5 mg. of the powder is dissolved in 1 ml. of a solution of 25 per cent ethyl alcohol in saline. It is given in one single

injection and perfusion is continued for 60 to 90 min. The flow rates are relatively low, primarily because of difficulty in obtaining an adequate venous return, especially if the vessels are small. After completion of the perfusion, the region is washed out with 500 cc. of dextran, followed by 500 cc. of whole fresh blood. The blood vessels are closed and an antiheparin drug (Polybrene‡) is administered intravenously.

Perfusion of the lower extremities. The lower extremities may be perfused through three levels: the popliteal, femoral and iliac. Usually, catheters nos. 10, 12 and 14 are employed.

Popliteal perfusion has been carried out chiefly as a primary procedure for cancers below the knee. For this purpose, the knee is flexed 45 degrees and a short longitudinal incision is made in the lower portion of the medial aspect of the thigh. A tourniquet is placed around the mid thigh.

The most advantageous level to perfuse the entire lower extremity is through the external iliac artery and vein, with the tips of the catheters lying just distal to the inguinal ligament; the agent is thus delivered to the entire extremity, including the important group of lymph nodes within the femoral triangle. The iliac vessels are approached extraperitoneally through a short oblique incision which divides the rectus muscle. The deep epigastric, deep circumflex iliac and obturator vessels are ligated in order to reduce leakage. An Esmarch bandage is used for a tourniquet, being wrapped tightly around the upper portion of the thigh and held in place by a Steinmann pin driven into the anterior-superior iliac spine.

For tumors of the lower extremity which tend to metastasize *via* the lymphatics, perfusion at the femoral level is performed as a second-stage operation subsequent to iliac perfusion. In such cases, the femoral perfusion is immediately preceded by femoral lymphadenectomy. Because of its simplicity femoral perfusion may also be

‡ Hexadimethrine bromide (Polybrene, Abbott) 1 mg. per 100 U.S.P. units of heparin.

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† Pulmo-Pak disposable bubble oxygenator (Abbott).

employed as a primary procedure for tumors of the lower extremity which do not tend to metastasize via the lymphatics. The Esmarch tourniquet is applied as for the iliac perfusion.

Axillary perfusion. In the absence of clinically positive axillary lymph nodes, axillary lymphadenectomy usually is omitted and perfusion is carried out through a short infraclavicular muscle-splitting incision. The proximal portions of the axillary artery and vein are incised, and the tips of the catheters are passed to the region of the insertion of the deltoid muscle. A tourniquet is applied proximally.

If the axillary lymph nodes are enlarged clinically, both the axillary contents and the arm are perfused. The incision is begun at the medial end of the clavicle and curved downward and outward to the posterior axillary line. The first portion of the axillary vessels are again incised, and the tips of the catheters are inserted down to the third portion of the axillary artery and vein. This procedure is followed immediately by radical axillary lymph node dissection. We have no suitable tourniquet for perfusion at this level.

Pelvic perfusion. In this institution the pelvis has been perfused for tumors of the rectum, prostate, bladder, vulva, vagina and perineum, all of which were inoperable and not amenable to radiotherapy. The abdomen is opened through a midline incision extending from the xiphoid process to the symphysis pubis. This distal aorta and the vena cava are exposed for lesions supplied by the hypogastric arteries. Both common iliac arteries are incised for a short distance at the level of their bifurcation, and no. 10 catheters are passed into each hypogastric artery. The following vessels are occluded: (1) the posterior division of each hypogastric artery, (2) the lumbar veins and (3) the external iliac, ovarian or testicular, inferior mesenteric, and epigastric arteries and veins. The lower end of the vena cava is mobilized by dividing two or three lumbar veins, and a no. 20 catheter is inserted into the vena cava for the return flow of the agent. A tourniquet is then placed around the upper end of each thigh. The pelvic circuit may be altered according to the location and extent of the lesion.

Carotid perfusion. External carotid perfusion has been performed for lesions of the oral, nasal and pharyngeal cavities which were not amenable to surgical treatment or irradiation. Both sides of the neck are exposed through a curved incision

extending from mastoid process to mastoid process. As a rule, the superficial temporal, superior thyroid, occipital and posterior auricular vessels are temporarily occluded or ligated in order to reduce leakage. The external carotid artery on each side is used for delivery of the agent, and the common facial vein on each side of the neck, when present, for its return. In the absence of the common facial vein, the internal jugular vein is chosen for the return flow. A no. 10 catheter and a 13-gauge needle especially designed for this procedure are employed.

Local tissue tolerance and the leakage factor. In arriving at the ideal dose of the chemotherapeutic agent, we have previously pointed out that the two most important limiting factors are (1) local tissue tolerance and (2) the leakage factor.⁴ The local tissue tolerance is indicated by the amount of the drug which the normal tissues can tolerate without being permanently damaged. The leakage factor refers to the extent of cross circulation, expressed in percentages, between the region being perfused and the remaining portion of the body. In perfusion of the distal extremities there is virtually no leakage; thus, the only limitation to the amount of drug which can be delivered is the tolerance of the local tissues.

With respect to the leakage factor, clinical studies with the use of radioactive iodinated serum albumin (RISA) have enabled us to determine how efficiently the region being perfused has been isolated.⁵ By means of a scintillation probe, rate meter and rectilinear recorder, we are now able to monitor the leakage as it occurs and thus to determine the degree of isolation of the perfusion circuit before the chemotherapeutic agent is injected. As a consequence, we are better able to estimate the proper dosage of the chemotherapeutic agent and hence to preclude complications.

In the majority of patients, the leakage factor in a specific circuit is reasonably predictable. Unexpected variations are encountered, however, and in patients of this group continuous monitoring has proved an invaluable asset. No significant complication incident to leakage has developed since this new technique has been employed. As stated previously, no leakage is associated with perfusions of the distal extremities. In the iliac perfusion, the leakage factor usually varies from 10 to 20 per cent at the end of 1 hr.; in

TABLE 1

Recommended doses of nitrogen mustard (HN₂) and of phenylalanine mustard (PAM) in perfusion therapy for an adult

Level of Perfusion	HN ₂	PAM
	mg.	mg.
Aortic.....	30-50	50-75
Axillary.....	20-30	50-75
Iliac.....	25-40	75-125
Femoral.....	25-40	75-125
Popliteal.....	20-30	50-75
External carotid.....	20-30	50-75

pelvic perfusions it varies from 50 to 75 per cent, and in external carotid perfusions from 70 to 80 per cent.

Dosage. The doses of nitrogen mustard and phenylalanine mustard which we believe can be safely employed are shown in table 1.

Complications. The complications of perfusion may be classified as systemic and local. The most common systemic complication in our experience has been depression of the bone marrow from excessive leakage. In a number of patients this has been associated with a temporary loss of body hair. Several patients have exhibited toxic symptoms which appeared to be related to acute necrosis of the perfused tumor and absorption of the end products. These symptoms consisted of anorexia, malaise, nausea, vomiting, fever and tachycardia, of varying severity. In addition, three patients have had severe hypotension, possibly incident to acute necrosis, within 24 hours after the operation.

Complications related to local tissue tolerance have varied from simple erythema and mild edema to blistering and massive necrosis. One patient had extensive necrosis, necessitating a transmetatarsal amputation, following popliteal perfusion with 75 mg. of phenylalanine mustard, although this has been a fairly standard dose at this level. In perfusing patients with peripheral vascular disease, special caution should be observed. Often, the tissues will not tolerate the usual dose of the chemotherapeutic compound, and the amount should be reduced. Further, the manipulation of the catheters, the application of the tourniquet, and the effects of the drug itself may be responsible for premature amputation of a digit or amputation of an extremity. Pain in a perfused extremity immediately after operation is an ominous sign; almost without exception, it

has been associated with severe injury to normal tissues.

RESULTS

Of the 128 patients who have had perfusion, 2 died postoperatively. One of these developed hypotension within 24 hours and died 36 hours later. It is believed that death was related to acute necrosis of an extensive carcinoma of the vulva and groins, with absorption of the end products. The second patient died after external carotid perfusion, the fatality being caused by overwhelming sepsis probably incident to excessive leakage of the agent and depression of the bone marrow.

The most favorable response to perfusion has been exhibited by the melanomas. Because of the impressive changes observed both clinically and histologically, a clinical experimental program for treating patients with melanomas involving the extremities was begun in this institution 2 years ago.⁶ In view of the short period of observation, the results in this group of patients have no real value at present. The squamous carcinomas have responded least. Some of the sarcomas have undergone impressive gross and histologic changes. These have included one fibrosarcoma, one leiomyosarcoma, one lymphangiosarcoma, one chondrosarcoma, and one unclassified sarcoma. No material changes have been observed in the small group of osteogenic carcinomas. The vast majority of even the lesions which responded favorably, *i.e.*, the melanomas and sarcomas, have not been *completely* destroyed either clinically or histologically. A number of patients have reported relief of pain postoperatively, especially those with cancer of the head and neck regions.

DISCUSSION

We are constantly being asked, "Just what do you think of perfusion, and is it any good?" The answer is that one cannot be truly enthusiastic about the currently available chemotherapeutic agents, regardless of the method of administration. A significant number of patients, however, have received definite palliation from the procedure, *i.e.*, either a regression of the tumor or relief of pain, or both. At present, perhaps the major reason for pursuing this experiment is that perfusion serves as a medium for investigating human cancers. In our opinion, it is superior in several respects to known methods

of studying tumors in the laboratory animal. In the first place, one is dealing with spontaneous tumors in man, rather than with transplanted tumors in animals. Also, the correlation of the responses of tumors in animals with those in human beings following administration of specific drugs has been disappointing. For these and other reasons, perfusion has stimulated considerable interest in clinical cancer research, notably among surgeons. Whether the procedure is worthwhile as an adjuvant to the surgical treatment of patients with cancer cannot yet be determined.

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SELECTIVE PULMONARY HIGH CARCINOLYTIC AGENT CONCENTRATION IN THE TREATMENT OF BRONCHOGENIC CARCINOMA*

A PRELIMINARY EXPERIMENTAL REPORT

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Concentration of potentially carcinolytic agents in selected viscera or isolated parts of the body has been attempted by intravascular injections^{1, 3, 8, 9} and by perfusion of blood vessels with an extracorporeal circuit.⁶ Blades and Hall showed the lung capable of withstanding ischemia for a period of 15 minutes.^{2, 3, 4} They injected carcinolytic agents (nitrogen mustard, sulfa mustard, triethylene thiophosphoramide (thioTEPA) and oxapentaethylene phosphoramide (MEPA) into the pulmonary arteries of dogs. They trapped the agent used in the lungs for 15 minutes by occluding all the vessels in the hilum of the lung. In general, the adverse local effects defeated the carcinolytic action of the chemicals. However, there was evidence that the undesirable general effects of the drugs on the body as a whole were reduced. Preliminary experiments with tagged sulfa mustard suggested high concentration of the drug is retained in the lung after the temporary occlusion of the blood supply is released. Other carcinolytic drugs are probably likewise retained. When nitrogen mustard is administered intravenously, the drug is very promptly removed from the blood stream and reacts quickly with the tissues. Within a few minutes after injection, nitrogen mustard undergoes chemical transformation, combines with reactive compounds, and is no longer present in active form. No doubt it is

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this retention of these drugs, trapped in the lung temporarily by occlusion of the pulmonary vessels, which accounts for the lack of demonstrable effects on the hemopoietic system as manifested by hemologic studies (fig. 1).

It has long been suspected that failure of surgical cure is at times the direct result of dissemination of neoplastic cells during surgical procedures. In bronchogenic carcinoma cases, it is generally accepted that prognosis can be more reliably based on whether or not malignant cells are found microscopically in the lymphatic and vascular channels of the tumor rather than on the type of neoplastic cell present or on the presence or absence of local lymphatic metastases. The presence of cancer cells in peripheral blood, with an increase in numbers during surgical manipulations, has been demonstrated by Cole, Roberts and others.^{5, 11} Malignant cells in the peripheral systemic blood were usually single, whereas those found in the major venous trunks draining the tumor site were generally in clumps. Animal experiments indicated that nitrogen mustard and thioTEPA would prevent the "take" of such cells when given within a few minutes to an hour after their inoculation.

We were not cognizant of the report of Blades and Hall³ of a somewhat similar experiment at the time we performed our studies. They concluded that nitrogen mustard was so destructive to lung tissue that it would not be feasible to employ the drug either experimentally or in the human subject. They found TEPA and sulfa mustard produced similar fatal results, and concluded that MEPA was best tolerated by the experimental animals. Our studies have been limited to nitrogen mustard,† which, as the most

† Nitrogen mustard in our experiments was used in the form of Mustargen supplied by Merck Sharp & Dohme.

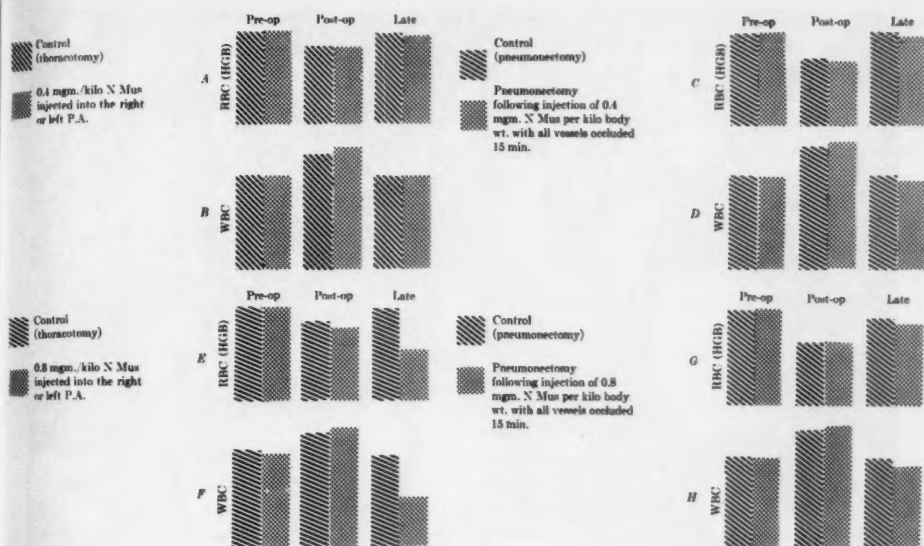


FIG. 1

TABLE 1

*Nitrogen mustard injection into right or left pulmonary artery**

Dog No.	Nitrogen Mustard Injection mg./kg.	Results
1	0.4	Lived
2	0.4	Lived
3	0.8	Lived
4	0.8	Lived

* No occlusion of vessels.

destructive of these drugs, provides the most formidable test of this type of experimental procedure. Although our results are in agreement with those of Blades and Hall, our conclusions, based on additional experiments, differ as to the potentialities of the use of this drug.

EXPERIMENTAL STUDIES

Injections of nitrogen mustard into the right or left pulmonary artery or segmental branches of dogs through a cardiac catheter or during thoracotomy in dosages proportionately accepted for human intravenous injection were tolerated by the animals without harmful effects on the lungs (table 1). No greater depression of the hemopoietic system resulted than it did with

TABLE 2

Nitrogen mustard injection into right or left pulmonary artery with pulmonary vessels occluded for 15 minutes

Dog No.	Nitrogen Mustard Injection mg./kg.	Results
5	0.4	Died (within 24 hr.)
6	0.4	Died (within 24 hr.)
7	0.3	Died (within 24 hr.)
8	0.3	Died (within 24 hr.)
9	0.2	Died (within 24 hr.)
10	0.2	Died (within 24 hr.)
11	0.1	Died (within 24 hr.)
12	0.1	Died (within 24 hr.)

control animals undergoing thoracotomy without nitrogen mustard injections (fig. 1, A and B) or with the usual method of intravenous administration of nitrogen mustard several days post-operatively.

Retention in the lungs for 15 minutes by temporary occlusion of the hilar vessels of even small amounts of nitrogen mustard injected into the right or left pulmonary artery consistently resulted in death of the animal in a matter of hours (table 2) from acute inflammation of the treated lung (fig. 2). Other methods which

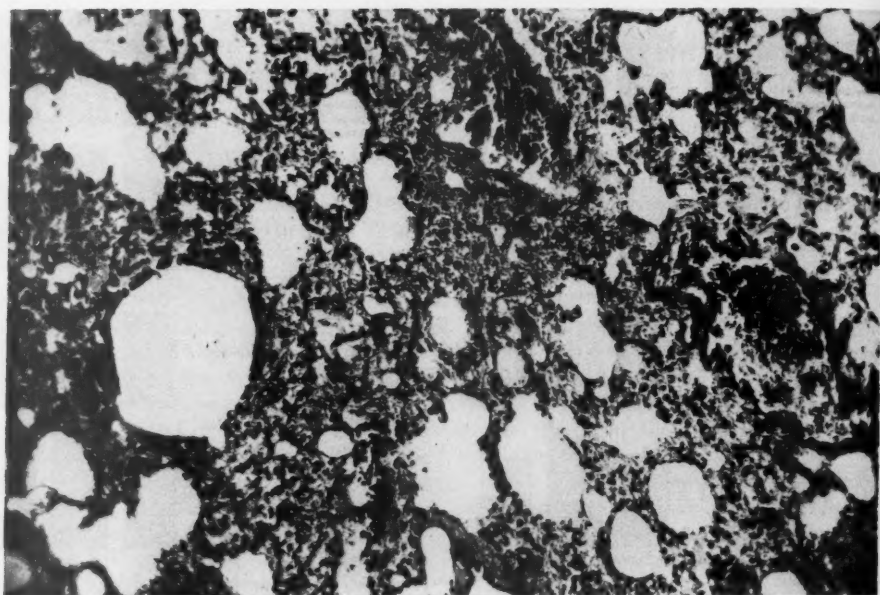


FIG. 2. Microscopic section of lung with acute necrosis, bronchitis and hemorrhagic pneumonia as a result of treatment with nitrogen mustard.

TABLE 3

Nitrogen mustard injection into right or left pulmonary artery with pulmonary vessels temporarily occluded*

Dog No.	Period of Occlusion	Results
	min.	
5	15	Died (within 24 hr.)
6	15	Died (within 24 hr.)
13	10	Lived
14	10	Died (10 days postoperative)
15	5	Died (within 24 hr.)
16	5	Lived

* 0.4 mg./kg.

TABLE 4

Nitrogen mustard injection into right or left pulmonary artery with pulmonary veins occluded 15 minutes

Dog No.	Nitrogen Mustard Injection	Result
	mg./kg.	
17	0.4	Died (3rd postoperative day)
18	0.4	Died (5th postoperative day)

TABLE 5

Nitrogen mustard injection into right or left pulmonary artery with pulmonary artery and veins occluded 15 minutes and then ligated

Dog No.	Nitrogen Mustard Injection	Results
	mg./kg.	
19	0.4	Died (within 24 hr.)
20	0.4	Died (within 24 hr.)
21	0.3	Died (within 24 hr.)
22	0.3	Died (within 24 hr.)
23	0.2	Died (within 24 hr.)
24	0.2	Died (within 24 hr.)
25	0.1	Died (within 24 hr.)
26	0.1	Died (within 24 hr.)

retained the drug in the lung, varying periods of time almost always resulted in death of the animal in a matter of hours to days (tables 3 to 5). However, when the pulmonary vessels were occluded only 5 or 10 instead of 15 min. after injection of 0.4 mg. of nitrogen mustard per kg. of body weight, the animals survived or survived longer periods of time (table 3). These results have led the authors to consider the possibility

TABLE 6

Pneumonectomy after nitrogen mustard injection into right or left pulmonary artery with pulmonary artery and pulmonary veins occluded 15 minutes

Dog No.	mg./kg.	Results
27	0.1	Lived
28	0.1	Lived
29	0.2	Lived
30	0.2	Lived
31	0.3	Lived
32	0.3	Lived
33	0.4	Lived
34	0.4	Lived
35	0.8	Lived
36	0.8	Lived
37	1	Lived
38	1	Died (3rd postoperative day)
39	2	Died (1st postoperative day)
40	4	Died (2nd postoperative day)

that shorter periods of occlusion, possibly with smaller doses of the carcinolytic drug, may be tolerated without removal of the lung.

If pneumonectomy was performed immediately after release of the temporary occlusion after such injections, the hilar structures showed good healing, and the animal survived (table 6). This occurred in animals in which occlusion was maintained for 15 min. with as much as 1 mg. of nitrogen mustard per kg. of body weight. Furthermore, the depression of the hemopoietic system was less pronounced as shown by comparison with controls (fig. 1, C, D, G, and H) or comparison with animals given the same amount of nitrogen mustard by the presently more accepted general intravenous route.

HEMATOLOGIC STUDIES

Hematologic studies in animals receiving injections of 0.4 mg. nitrogen mustard per kg. without occlusion of the pulmonary vessels resulted generally in a slight fall in hemoglobin determinations postoperatively, but this returned to normal 4, 6 and 8 weeks postoperatively without any special treatment. Animals undergoing pneumonectomy after similar injections with temporary occlusion of the pulmonary vessels also showed an immediate fall in hemoglobin levels after operation with normal or slightly decreased levels in 4, 6 and 8 weeks. In both of the above experiments, there was an

immediate postoperative leukocytosis with the Schilling differential count shifting to the left. The animals receiving merely injections of the drug showed a return to normal over periods of 4, 6 and 8 weeks, whereas the pneumonectomized dogs showed a slightly slower return to normal as far as the white blood cells were concerned. In each of the above experiments the platelet counts remained essentially unchanged. Hematologic studies after injection of nitrogen mustard into the right or left pulmonary artery with or without occlusion of the hilar vessels compared very favorably with control dogs undergoing simple thoracotomy and pneumonectomy, respectively (fig. 1, A to D).

Animals receiving injections of 0.8 mg. nitrogen mustard per kg. of body weight eventually showed a much greater decrease in all hemopoietic elements as compared with animals undergoing pneumonectomy after injection of a same amount of drug with temporary occlusion of the vessels (fig. 1, E to H). This would indicate that retention of the drug in the lung following a period of temporary occlusion of the vessels prior to pneumonectomy spared the remainder of the body from much of the injected chemical.

DISCUSSION

It is postulated that carcinolytic agents could be used more effectively in the treatment of bronchogenic carcinoma by obtaining higher concentrations of the agent in the involved viscera than is possible by the more accepted route of general intravenous administration. The lung lends itself well to such selective administration into the right or left pulmonary artery or even into the arterial branch supplying the involved lobe or segment.

In obviously inoperable cases it is suggested that the drug be injected into the vessels of the involved lung by means of cardiac catheterization techniques. Thus, in a case of bronchogenic carcinoma manifesting the superior vena cava compression syndrome, the drug could be introduced through a cardiac catheter into the right pulmonary artery at or near the superior pulmonary trunk. Milligram for milligram, a greater concentration of the carcinolytic drug can thus be secured in the area of the malignant neoplasm. Selective localized injection of carcinolytic drugs would permit effective palliative results with smaller dosages than are now administered by

general intravenous injection. The generalized (hemopoietic) effects would therefore be reduced, permitting therapy more frequently if necessary.

In resectable cases it is suggested that the carcinolytic drug might be injected into the pulmonary artery of the involved lung (or possibly into the arterial branch supplying the involved portion of the lung) and the hilar vessels occluded for 15 minutes or more prior to undertaking the vigorous manipulations often necessary in performing a pneumonectomy or lobectomy. Some modification of surgical technique (such as operating upon the patient in the supine position and occluding the pulmonary veins inside the pericardial sac) will be necessary to accomplish this. Judging from the results of our animal experiments, this would permit use of a larger dose of the carcinolytic drug with no more and probably less toxic effects on the hemopoietic system and the body in general than when the drug is used intravenously by its present method of administration into the general circulation.

It is postulated that the injection of carcinolytic drugs into the pulmonary artery at time of operation will reduce the incidence of metastases which probably occur as a result of the manipulations of the lung during resection.

The authors believe that shorter periods of occlusion of the pulmonary vessels with retention of small doses of nitrogen mustard may be tolerated without removal of the lung. This possibility, however, requires further investigation.

SUMMARY

1. Injection of nitrogen mustard into the right or left pulmonary arteries (or their segmental branches) of dogs during thoracotomy in dosages proportionately accepted for human intravenous injection in carcinoma cases were tolerated by the animals without obvious harmful effects on the lungs generally. No greater depression of the hemopoietic system resulted as compared with the usually accepted method of intravenous administration several days postoperatively. Injection by means of cardiac catheterization technique was likewise tolerated.

2. Retention in the lungs for 15 minutes by temporary occlusion of the hilar vessels of even small amounts of nitrogen mustard injected into the pulmonary artery consistently resulted in

death of the animal from acute inflammation of the treated lung. However, if pneumonectomy was performed immediately upon release of the temporary occlusion following injection of even a moderately large dose of the carcinolytic drug, the hilar region showed good healing, the animal survived, and the depression of the hemopoietic system was less pronounced than when a similar amount of nitrogen mustard was given by the presently more accepted general intravenous route.

3. Occlusions for shorter periods of time following injection of small doses of the carcinolytic drug into the pulmonary artery with the hilar vessels temporarily clamped may possibly be tolerated by the experimental animal without pneumonectomy. Further investigation of this possibility is indicated.

4. Possible clinical applications are suggested.

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ADDENDUM

Since preparation of this paper the authors have learned that Drs. James F. Morris and

Leonard M. Goldberg of Portland, Oregon, at the 1960 meeting of the Northwest Society of Clinical Research, reported favorable radiographic response, in terms of tumor-mass reduction or improved lung aeration, in patients injected with nitrogen mustard by cardiac catheter into a branch of the pulmonary artery leading to the region of a bronchogenic carcinoma. Drs. Nicholas P. D. Smyth and Brian Blades at the 1960 meeting of the American Association for Thoracic Surgery reported selective chemotherapy of the lung during unilateral pulmonary arterial occlusion with a balloon tipped cardiac catheter.

Further studies in our laboratory suggest, with modifications of the techniques described, a "chemical pneumonectomy" is a possibility.

PARIUM CONTAMINATION OF THE PERITONEUM THROUGH PERFORATED PEPTIC ULCER

REPORT OF FOUR CASES

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Barium contamination of the peritoneal cavity through a perforated peptic ulcer is a rare event. Rosenthal, cited by Gross,³ was the first to record, in 1916, the perforation of a peptic ulcer occurring in a patient on the x-ray table when the barium was seen in the lesser peritoneal cavity. Schilling,⁷ in 1946, was able to collect 57 cases in the literature and added one of his own. He made interesting observations with regard to the immediate course and to the later disposal of the contrast substance in the peritoneal cavity.

According to the cases reported in the literature, most peptic ulcers that have perforated in relation to barium contrast meal have perforated a few hours or days after the ingestion of the medium. In these instances there is actually little barium contamination of the peritoneal cavity. Schilling's⁷ review revealed that only a few cases were observed fluoroscopically at the time of perforation. Some found a significant relationship between perforation of peptic ulcers and the barium meal roentgenographic examination. Singer,⁸ Schilling⁷ and Eckman,² working independently, found that less than 1 per cent of all perforated peptic ulcers occurred during or after ingestion of barium sulfate and that the incidence of perforation following the examination of all unruptured peptic ulcers was 0.08 of 1 per cent.⁸

Four cases of peptic ulcer, two perforating immediately before and two after the administration of barium contrast meal, have been personally observed and followed for 8 months to 5 years. These are reported for the purpose of discussing the operative management, studying the postoperative course and recording the immediate and later fate of barium in the peritoneal cavity.

Presented at the 12th Annual Meeting of the Southwestern Surgical Congress, Las Vegas, Nevada, March 28 to 31, 1960.

CASE REPORTS

Case 1. B. S., a 38-year-old woman, was admitted to the hospital at 10:45 a.m. on March 7, 1957, as an emergency. She was pulseless, cyanotic, her blood pressure could not be recorded and her abdomen was boardlike. The history revealed that she had had many bouts of pain in the epigastrium with vomiting during the past year. The pain was most pronounced $\frac{1}{2}$ to 1 hour after meals and was partially relieved by vomiting. These episodes lasted for from 5 to 8 days and the patient felt perfectly well between the periods of pain. This illness, however, had begun 3 weeks before admission and was marked by unusually severe pain. She vomited many times during this episode and the material frequently contained bright red blood. She consulted her family physician the day before admission and he referred her to a radiologist for an upper gastrointestinal tract roentgenogram. She was given 1 oz. of barium sulfate with directions to swallow it in water at 5:00 a.m. the day of the examination. She retired feeling fairly well but was awakened at 2:00 a.m. the morning of admission with acute abdominal pain. This was not relieved by hot packs and aspirin. However, she took the barium at 5:00 a.m., as instructed, and reported to the radiologist at 9:00 a.m. She appeared acutely ill and in a state of semishock. Studies of the abdomen with the patient supine, erect and in a lateral decubitus position were made immediately (fig. 1). These roentgenograms demonstrated evidence of a perforated viscus with a large amount of free air beneath the right hemidiaphragm. There was widespread barium extravasation into the peritoneal cavity. The barium was seen outlining the liver, spleen and both lateral gutters. The patient was given norepinephrine intravenously and prepared for surgery.

At operation, the abdomen was entered through a right rectus incision, and copious amounts of barium and dirty fluid exuded from the peritoneal cavity. There was a large, perforated gastric ulcer high on the anterior wall of the stomach. The perforation was about 1 cm. in diameter and

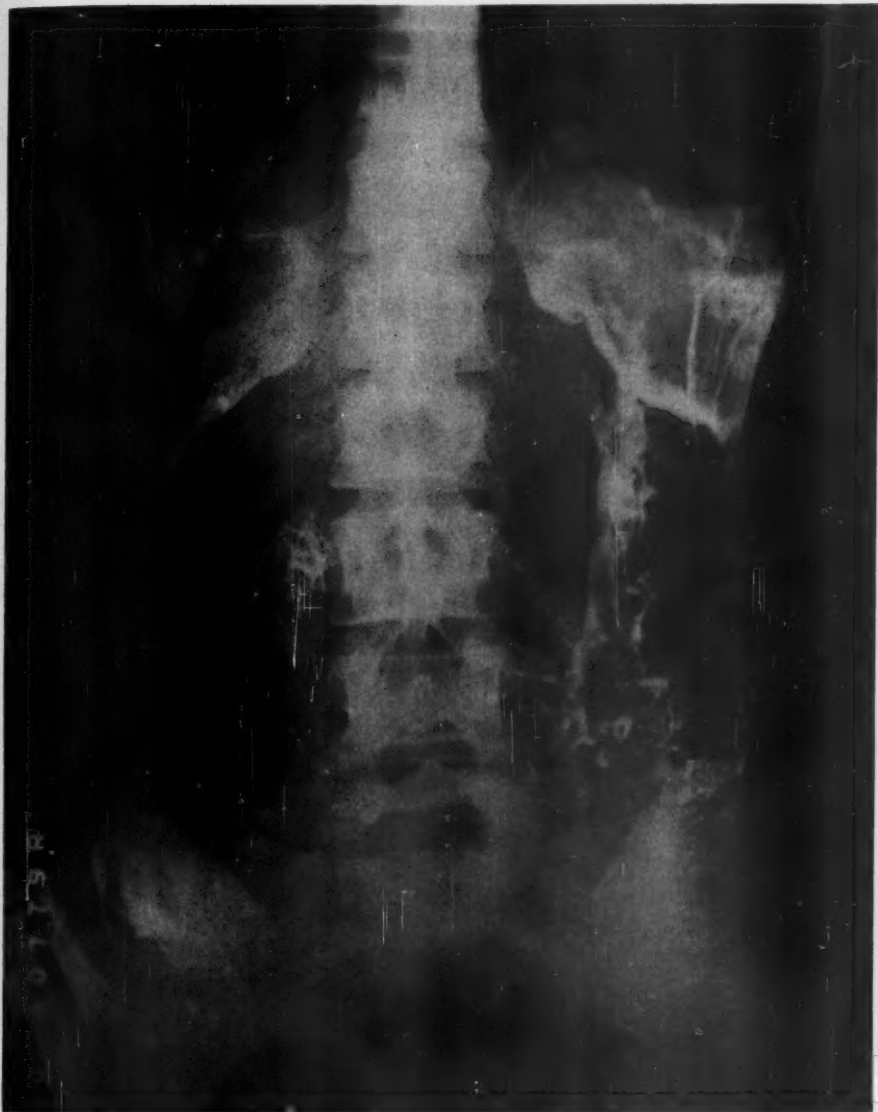


FIG. 1

barium exuded from it. A subtotal gastrectomy was performed and gastrointestinal continuity was re-established by use of the Hofmeister modification of the posterior Polya procedure. Two drains were placed in Morison's pouch and brought out through a stab wound lateral to the incision. Tension sutures were placed and the abdomen was closed in layers.

The patient's convalescence was marked by minimal left basilar pleural effusion which cleared up without external drainage. She was discharged from the hospital on the 8th postoperative day.

A flat plate of the abdomen made 6 months after the operation revealed the following: The barium had been fixed about the spleen, the liver and both lateral gutters. Lesser amounts of



FIG. 2

barium were seen in the pelvis and throughout the abdomen. The extent and distribution of barium had not changed when a film of the abdomen was taken 3 weeks after surgery, on March 22, 1957 (fig. 2).

Comment. This patient had more extensive peritoneal contamination by barium than

occurred in any of the other three cases presented below. This was probably due to the location of the ulcer on the anterior wall of the stomach. The ulcer had perforated prior to the ingestion of barium and, as was also true in case 2, there was no cause and effect relationship between the perforation of the ulcer and the upper gastrointestinal examination.

Although the patient's peritoneal cavity was grossly contaminated with barium and her general condition poor, subtotal gastrectomy was deemed the operative procedure of choice for treating the pathology encountered. The malignant potential of an ulcer on the anterior surface of the stomach and the technical difficulties anticipated in closing a large perforation, as was encountered here, made a definitive procedure obligatory.

Case 2. R. H., a 60-year-old man, was admitted to the hospital on March 24, 1952, with the complaint of frequent episodes of indigestion over the previous 2 or 3 years. Three days before this admission he had developed rather acute abdominal pain and vomiting. The vomitus contained blood. On admission to the hospital, physical examination revealed a tender and rigid abdomen. The white blood count was 25,350; hemoglobin, 16 gm. An upper gastrointestinal roentgenogram was ordered, and on March 25, during fluoroscopy, the radiologist detected barium escaping into a sac-like structure, indicating that a perforation was present. The point of perforation was not visualized, but it was

assumed that the collection of barium was in the lesser peritoneal space. The roentgenograms revealed a large collection of barium in the lesser omental space and about the duodenum (fig. 3). The patient had less discomfort than on the day of admission.

On March 26 the abdomen was opened through a transverse incision. Externally, the stomach appeared to be normal. The lesser peritoneal cavity was opened and a cloudy-appearing material was found. This material was a mixture of barium and intestinal contents. There was a perforated ulcer on the posterior aspect of the duodenum in its second portion. The duodenum was mobilized and the common bile duct was found to enter the duodenum about 0.5 cm. distal to the ulcer. The ulcer was closed with a free omental graft. The duodenum was divided proximal to the ulcer and the stump was inverted with two layers of gastrointestinal suture and one of cotton musculoserosal suture. A high subtotal gastrectomy was performed and gastrointestinal continuity was re-established by use of the Hofmeister modification of the posterior Polya procedure. The transverse mesocolon was sutured to the stomach proximal to the anastomosis. Two Penrose drains were placed in Morison's pouch



FIG. 3



FIG. 4

and one in the lesser peritoneal cavity. These were brought out through a stab wound. The abdomen was closed in layers with fine catgut and silk. Tension sutures were used.

The patient's postoperative course was quite stormy. He developed a duodenal fistula on the 8th postoperative day and a toxic psychosis on the 16th postoperative day. Suction was applied to the fistula through a sump drain. The fistula gradually subsided and closed. He left the hospital on May 6, 1952, and has had no gastrointestinal complaints since. A roentgenogram of the abdomen taken 5 years after the operation revealed scattered droplets of barium fixed in the lesser peritoneal cavity (fig. 4).

Comment. From the clinical history and findings, and the immediate evidence of barium spill on fluoroscopic examination, we feel that this patient's ulcer had perforated before upper gastrointestinal roentgenographic study. Perforation with barium contamination of the lesser peritoneal cavity is extremely rare, as most perforated posterior wall duodenal ulcers will become embedded in a neighboring organ. While

there was evidence of extensive barium spillage into the lesser peritoneal cavity on initial roentgenographic studies, only a few droplets were seen on the 5-year follow-up study. It is felt that most of the barium, along with gastric contents, had been aspirated from the lesser peritoneal cavity at the time of surgery.

Closure of this ulcer was difficult because of its proximity to the opening of the common bile duct into the duodenum. Subtotal gastrectomy, an operation affording the opportunity for a permanent cure of the ulcer, was carried out because the patient was in good condition during the operation.

Case 3. E. K., a 52-year-old man was admitted to the hospital on October 21, 1953, on an emergency basis. He complained of severe pain in the epigastric area of 4 to 6 hours' duration. His teeth had been extracted about 1 month before this episode, and since that time he had been unable to eat solid foods. During the previous 2 weeks the patient had suffered nonspecific distress with nausea and vomiting. The history revealed that he had had 3 similar attacks, the first appear-

ing in 1936. Between episodes he had been entirely well. Eight hours before the present admission to the hospital a gastrointestinal tract roentgenogram had been made with barium sulfate ingested as the contrast substance. The examiner reported the presence of an obstructing duodenal ulcer in the first portion of the duodenum. On physical examination a board-like abdomen with no

bowel sounds was noted. Roentgenograms of the abdomen in supine, lateral decubitus and upright positions, taken shortly after hospital admission, demonstrated a moderate amount of free intraperitoneal air. A small amount of extravasated barium was seen outside the stomach in the right upper quadrant of the abdomen. (fig. 5).

The white blood count was 12,250; hematocrit,



FIG. 5

52 per cent. The patient was moved to the operating room after the last roentgenogram was taken. The abdomen was entered through an upper left paramedian incision. A moderate amount of barium and fluid was found in the subhepatic space. The entire area had a thin, almost purulent membrane covering it. A 3-mm. perforation was found on the anterior portion of the first part of the duodenum. A subtotal gastrectomy was performed, preserving about 25 per cent of the stomach. Gastrointestinal continuity was re-established by use of the Hofmeister modification of the posterior Polya procedure. Tension sutures were placed and the abdomen was closed in layers. The patient's postoperative course was uneventful, the highest temperature being 100° on the 4th postoperative day. He was discharged from the hospital on November 1, 1953, and has remained well since. A roentgenogram made on April 15, 1957, revealed a few droplets of fixed barium beneath the liver margin.

Comment. Clinically, the patient had a chronic, obstructing duodenal ulcer. This was borne out by the upper gastrointestinal roentgenographic studies. At the time of these studies, no evidence of perforation was noted, either fluoroscopically or roentgenographically. Perforation apparently occurred 2 to 4 hours after the roentgenographic examination. Hence, this case falls into the same class as the majority of cases reported in the literature, in which perforation was known to occur sometime after the roentgenographic study. The relationship of the perforation and examination can only be speculated upon. This patient had an obstructing duodenal ulcer, and it is conceivable that vigorous attempts on the part of the examiner to outline the lesion may have led to perforation. Apparently protective pylorospasms followed perforation, since there was little contamination of the peritoneum with barium as seen on roentgenographic studies of the abdomen made immediately prior to surgery.

This perforated duodenal ulcer fulfilled the criteria ideally for primary resection at the time of perforation. The interval following perforation was short, the operation presented no technical difficulties, and the patient was in excellent physical condition.

Case 4. L. S., a 70-year-old man, was admitted to the hospital at 1:00 a.m. on January 13, 1950, complaining of severe upper abdominal pain of 5 hours' duration. The patient had not been feeling well for many months. He had lost weight,

had a poor appetite and frequently complained of epigastric pain which was not relieved by food or bicarbonate of soda. An upper gastrointestinal roentgenogram had been made at a radiologist's office about 12 hours before this hospital admission. An obstructing duodenal ulcer was demonstrated. Later that evening he developed severe upper abdominal pain which became excruciating. He had almost lost consciousness. When admitted to the hospital he was cold and cyanotic and he spoke incoherently. Examination revealed a dehydrated, very ill man with cold, clammy skin. His abdomen was distended and rigid. Some hyperactive bowel tones were present. Laboratory studies revealed the hemoglobin to be 7.5 gm. and white blood count 8350. Urinalysis was normal. A flat plate of the abdomen showed the stomach to be partially filled with barium and both the small and large intestines contained some barium. There was a moderate amount of free air, and there were flecks of barium beneath both leaves of the diaphragm. These roentgenograms have since been destroyed.

The patient was prepared for surgery. The abdomen was opened through an upper left paramedian incision. When the abdomen was entered, a great deal of dirty-colored, bile-stained fluid and barium exuded from the abdominal cavity. Barium covered the stomach, the greater omentum and the transverse colon. There seemed to be a small collection of barium in the upper part of the right peritoneal gutter. There was a large, penetrating duodenal ulcer which almost severed the pylorus from the duodenum. A high, subtotal gastrectomy was performed. The duodenal stump was inverted with two layers of gastrointestinal suture, and gastrointestinal continuity was re-established by use of the Hofmeister modification of the posterior Polya procedure. The free fluid was aspirated from the peritoneal cavity. Two Penrose drains were placed in Morison's pouch and brought out through a stab wound lateral to the incision. The abdomen was closed with tension sutures, catgut and silk. The patient left the operating room in good condition. He had a partial heart block which persisted, but caused no difficulty.

He developed a prostatic obstruction on the 10th postoperative day, shortly after the removal of his retention catheter. A transurethral prostatectomy was performed. The patient left the hospital in good health on the 21st postoperative day. He remained well until 3 years after the procedure, when he expired suddenly from a cardiac complication.

Comment. This patient, as in case 3, had an obstructing duodenal ulcer with perforation,

apparently following the upper gastrointestinal examination within a period of hours. One can, again, only speculate on the relationship of the fluoroscopic procedure to the perforation. As in case 3, it is conceivable that vigorous palpation was used to push the barium through the obstructed duodenum during fluoroscopy, with resultant weakening of the ulcer wall and perforation.

Peritoneal contamination by the stomach contents was not extensive even though, at exploration, the perforation was found to be so large that it almost severed the proximal part of the duodenum. This further illustrates the protective pylorospasm following perforation of a duodenal ulcer. The pathology found in this case presents another indication for primary, subtotal gastric resection at the time of perforation of a peptic ulcer. This patient's condition was precarious, but the findings at operation left no choice except to resect the stomach.

Clinical findings. The findings of 5 observers who have studied the fate of barium within the peritoneal cavity are summarized below.

Schilling⁷ injected 50 cc. of an unsterile barium sulfate suspension into the peritoneal cavities of 3 live dogs. This suspension, containing 40 gms. of barium sulfate, was injected through a 16-gauge needle into the right superior quadrant with the dog under Nembutal anesthesia. The dogs were extremely ill for 1 week. They refused food, drank little water and retched and vomited frequently. Roentgenograms taken 1, 2 and 3 hours following the injection revealed the barium to be widely diffused throughout the peritoneal cavity. It was most dense at the site of the injection. Postmortem studies revealed the barium sulfate encapsulated by dense, fibrous omental adhesions. Small deposits were observed through all portions of the peritoneal cavity. Particles were adherent to the diaphragm, bowel loops, liver, kidneys, spleen and urinary bladder. Schilling found that wherever barium particles were present, there were also dense adhesions that required sharp dissection for separation. The mesenteric lymph nodes contained barium and he was able to demonstrate, by a roentgenogram of the thorax, that the phagocytosed barium had migrated to the lymph nodes of the dog's thorax. On microscopic section, small particles of barium were observed, surrounded by round cell infiltration and a marked fibrocytic cell response with ingestion of barium particles.

Foreign-body giant cells were also noted. The lymph nodes showed hyperplasia of the lymphoid and reticulo-endothelial tissue. In some instances the structure of the lymph node was destroyed by a stuffing of the sinusoids with macrophages filled with refracted barium particles.

This confirmed the work of Himmelmann⁵ and Thomas,⁹ who also observed early widespread diffusion of the barium and marked lymphocytic response, then, later, encapsulation with granulation tissue. Paas,⁶ in more extensive experiments, found that pylorospasm occurred after perforation of the duodenum in dogs. It was stated that there was a marked delay in contamination of the peritoneal cavity with barium contained in the stomach under such circumstances. This delay was often more than 5 hours, compared with the rapid contamination occurring after perforation of the stomach. Paas observed that there was a much higher mortality after perforation of the stomach than after perforation of the duodenum.

Both Schilling⁷ and Hayden⁴ have recorded the clinical course in the follow-up roentgenographic findings in their cases with barium meal contamination, and support the observation of others that (1) barium in the peritoneal cavity quickly becomes fixed by fibrous exudate and (2) there is a peritoneal mechanism—pylorospasm—associated with acute perforation of a duodenal ulcer which limits extravasation and makes for better prognosis. This observation was also made by Paas,⁶ who concluded that barium in the peritoneal cavity may be left with safety.

We injected unsterile barium sulfate intraperitoneally into guinea pigs. All guinea pigs survived during a 6 weeks' observation period with no untoward effects other than a slight loss of weight. On postmortem study the findings were similar to those of Schilling⁷ both grossly and histologically. They were essentially those of a granulomatous, foreign body type of reaction without acute inflammatory change.

DISCUSSION

In 2 of the 4 cases presented there may well be a more than casual relationship between perforation of the duodenal ulcers and x-ray examination of the patients' upper gastrointestinal tracts. Both patients had obstructing duodenal ulcers. It is possible that vigorous attempts on the part of the examiner to push the barium through the pylorus to outline the ulcer may have

resulted in weakening of the ulcer bed and subsequent perforation. The factors of manipulation and compression during fluoroscopy of a stomach obstructed by a chronic duodenal ulcer was stressed in all 4 cases reported by Singer.⁸

In the other 2 cases, all clinical and roentgenographic evidence indicated that the ulcers had perforated prior to the oral ingestion of barium. The perforation of an ulcer during fluoroscopy must be exceedingly rare, there being few cases reported in the literature.^{1, 4} That others have occurred and have not been reported would seem likely.

On the basis of our experience we would agree with others that there must be a protective pylorospasm following perforation which limits the degree of extravasation. This was borne out in cases 3 and 4, in which there was only limited barium contamination as evidenced by preceding and follow-up roentgenographic studies. In case 2 there was contamination of the lesser peritoneal cavity only. More widespread contamination is likely to follow perforation of a gastric ulcer, as was evidenced in case 1.

From a surgical standpoint, a perforation related to the ingestion of barium sulfate should be operated upon as soon as possible, as is the case with any perforated viscus. The administration of vasopressor agents and other supportive measures used to treat the primary neurogenic shock should be employed while the preparation for operation is being carried out.

It is obvious, from the above observations, that we lay great emphasis upon a definite surgical procedure whenever this is possible. Choice of a procedure should not be influenced by the fact that barium has been added to the contaminating gastric contents. If the patient is in good condition and the procedure seems to be not too time consuming because of technical difficulties, subtotal gastric resection is the operation of choice.

Case 2 had the most complicated postoperative course of any of the cases treated, as a result of an attempt to brush the barium from the peritoneal surface. It is felt that the trauma caused to the peritoneum by attempting to remove the fixed particles is much more harmful and irritating than simply leaving the barium attached.

SUMMARY

From our experience and that of others, it would appear that many cases of barium con-

tamination secondary to perforated peptic ulcer could be avoided by strict adherence to the following: (1) Elimination of all palpation and manipulation during fluoroscopy when there is obvious obstruction of the stomach. Periodic film studies immediately following the fluoroscopic study will usually show the nature of the obstruction. (2) Removal of the barium following the examination by gastric lavage when obstruction is present. (3) Fluoroscopic check for air beneath the leaves of the diaphragm before the oral ingestion of barium.

In three of the four cases presented here, adherence to the above most certainly would have eliminated case 1, and would possibly have eliminated cases 3 and 4.

We can conclude from observations made in this series of cases that the progress and the postoperative course of a patient with perforated peptic ulcer is not influenced to any noticeable degree by the presence of barium sulfate contamination of the peritoneum.

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OMPHALOCELE TREATED BY A PURSE-STRING SUTURE

JESSE W. WHITE, M.D., F.A.C.S.

Pueblo, Colorado

I wish to present a method of repairing omphalocele by use of a purse-string suture. In reviewing the literature, I have found no mention of the use of such a method. Cresson and Pilling¹ have made a most complete review of the literature and apparently found no mention of this method.

Omphalocele, a rare congenital defect occurring in a ratio of 1:6600 births, is a herniation through the umbilical ring into the cord.¹ The resulting sac is composed of peritoneum and amniotic membrane with the umbilical vessels passing through the wall of the sac to the cord. The skin may extend outward on the sac for a short distance from the umbilical ring. It is the result of a variation from the normal development of the intestinal tract and abdominal cavity during the first 6 to 10 weeks of fetal life.² At the time of birth, the sac wall is thin and transparent and may contain only intestines or all of the abdominal viscera, depending on the size of the umbilical defect and capacity of the abdominal cavity. The diameter of the umbilical ring may vary from a few centimeters to a total absence of the abdominal wall. The sac may have a greater diameter than the umbilical ring and may have greater capacity than the abdominal cavity. Frequently, the cavity is too small to contain the viscera and primary closure of the defect is impossible. Any type of repair decreases an already inadequate abdominal cavity and replacing the extruded viscera adds a greater volume to the contents, causing increased abdominal pressure. This forces the diaphragm upward, thus decreasing the capacity of the thoracic cage and interfering with respiration. This pressure may cause the descent of inguinal hernias and interfere with the circulation of the blood through the abdominal organs, the aorta, and inferior vena cava. Fortunately, a baby's tissues are elastic and by stretching and rapid growth, compensate for this increased abdominal pressure.

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There are frequently other congenital defects.^{1, 2} Some are incompatible with life and require immediate treatment. Unless the omphalocele is treated, death is practically certain because of the rapid deterioration of the sac, permitting infection and peritonitis.

Gross has described a one-stage open operation for treating cases with a small enough defect to permit excision of the sac and approximation and suturing of the various layers of the abdominal wall.² For the larger defects, he has described a two-stage operation which has been used successfully.

I have used a method of treatment in two cases which consists of placing a purse-string suture through the umbilical ring around the opening of the omphalocele. The success of this procedure depends on the normal involution and evolution of the umbilical area that occurs in the first few weeks after birth and changes the anatomy to that of the more mature infant and adult.

ANATOMY OF THE ADULT

Between the rectus muscles of each side, the investing aponeuroses are firmly united into a dense tendinous band, the linea alba. The linea alba is composed mainly of the interlacing of the fibers which pass into it from the aponeurotic sheaths of the rectus muscles. At the umbilicus there is a circular opening encircled by dense fibrous tissue and filled with a thick connective tissue, extending from the subcutaneous tissue to the subserosa.³

The umbilical ring of the newborn is normally filled with cord tissue and vessels. The base is covered with peritoneum. This is shown in figure 1, which is a cross section through the middle of the umbilicus of a 2-day-old infant. Figure 2 shows a section through the inferior margin of the umbilicus. These show the relative density and strength of the fascia of the umbilical ring as compared to the various layers of fascia in the abdominal wall. They also show the continuity of the ring with the fascia layers of the abdomen.

After ligation, the cord tissue is rapidly re-

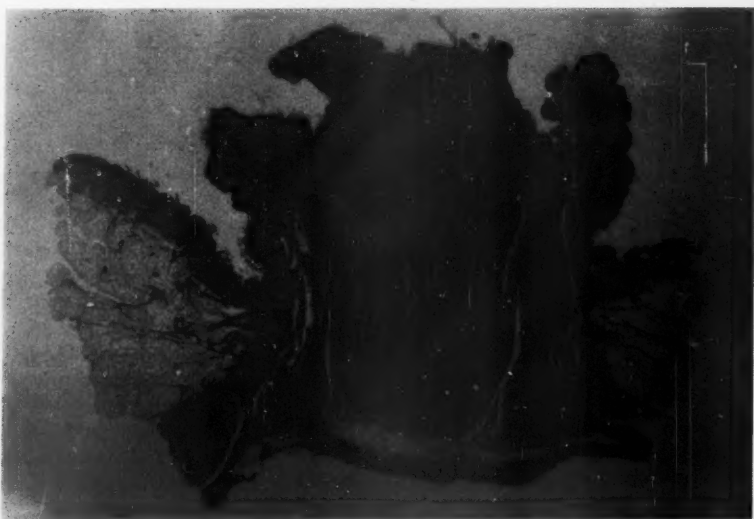


FIG. 1. Cross section through the middle of the navel of a 2-day-old infant, showing the umbilical ring filled with cord tissue and base covered with peritoneum. The left side from the bottom up shows peritoneum, inferior rectus fascia, rectus muscle, and superior rectus fascia, uniting to form the umbilical ring. It shows the subcutaneous fat and skin.

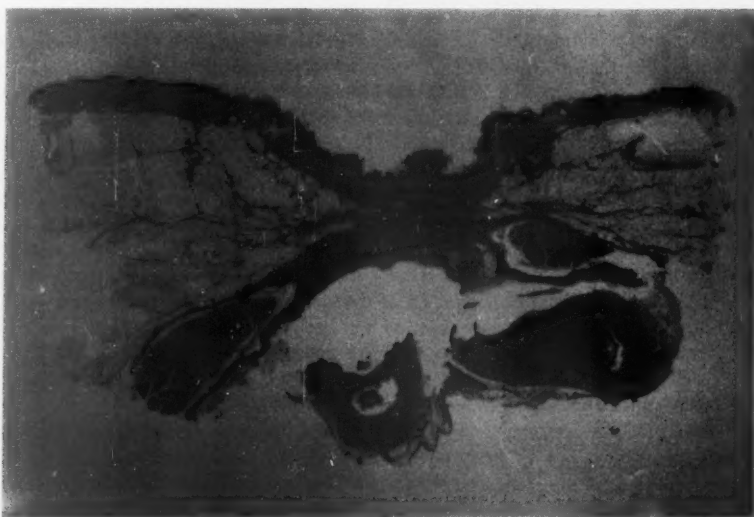


FIG. 2. A section through the inferior margin of the umbilical ring of the same infant, showing the union of the layers of fascia to form the umbilical ring.

placed by fibrous tissue. A purse-string contracts the large umbilical ring of an omphalocele around the base of the sac and cord vessels, and produces a condition similar enough to a normal ring and cord base to allow replacement by fibrous tissue. At the same time, the abdominal

wall grows to give a larger cavity in a relatively short time.

OPERATIVE PROCEDURE

Under drop ether anesthesia, a purse-string of nylon or strong silk (no. 5) is placed around the

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ring, using a cutting needle and dipping through the skin margin deep enough with each bite of the needle to enter the fascia of the ring. Next, the contents of the sac are reduced to the abdominal cavity. This is the most difficult part of the procedure. An assistant ventral flexes the baby's body, while the operator obliterates the sac by gently twisting the umbilicus and sac and, at the same time, kneading and applying pressure to the contents. It helps to apply gentle traction on the sac. It is necessary to use a thin layer of gauze over the cord and sac to prevent slipping of the slick sac during the twisting maneuver.

The purse-string can be placed first and the anesthetic given only during the reduction of the contents of the sac. As soon as the intestines are forced into the abdominal cavity, the purse-string is tightened and one knot tied. The sac is opened to make sure it is empty. If empty, the tying of the knot is finished. A secondary tie is placed distal to the purse-string and a clamp or tie should be placed on the cord near the apex of the sac. This last is a necessary precaution because bleeding may occur as a result of shrinking of the cord tissue.

I believe this procedure does not decrease the abdominal cavity as much as a primary closure



FIG. 4. Side view of case 1

by the usual method and it does not destroy any valuable tissue. Following the tying of the purse-string, the navel seems to heal as does the navel of a normal baby. It may take longer for the omphalocele cord stump to dry and separate than in the case of a normal umbilical cord. The larger the ring, the greater the diameter of the stump of the sac. I have treated two cases in this manner—both have healed well and I have not considered it necessary to do further surgery on the umbilical area.

CASE REPORTS

Case 1. A male child, born at term on April 2, 1945, had an intact omphalocele containing most of the intestines and stomach. The estimated diameter of the ring was 6 to 7 cm. About 3 hours after birth, I was asked to see the patient. Four hours after birth, he was given drop ether anesthesia and the defect closed with a purse-string of nylon. Several hours later, it was necessary to place an additional tie to control bleeding after the cord started to shrink. Pressure on the diaphragm produced considerable respiratory embarrassment, requiring oxygen for 8 days. He developed a large right inguinal hernia, and a smaller left one. The right threatened to strangulate at one time. The hernias were treated with a yarn truss and disappeared at the 4th month. He



FIG. 3. Front view of case 1

left the hospital when he was 31 days old. The sac and cord had not completely separated.

The umbilical stump was almost completely healed in 60 days, and entirely so in 75 days. His weight at birth was 5 lb. 10 oz. and at 3 months, 9 lb. 12 $\frac{3}{4}$ oz. Crying produced a bulging of the whole umbilical area.

The right inguinal hernia reappeared at the age of 4 years and was repaired. The left reappeared at the age of 13 years and was repaired. At this time the umbilical region appeared quite firm, although it bulged on straining. The recti muscles were widely separated and the attachments to the costal margins were also widely separated.

Figures 3 and 4 show him at nearly 15 years of age. He leads a normal life, is not hampered in activities usual to his age, and he does average school work.

Case 2. A male child was born at term on March 1, 1958. He seemed normal except for a large intact omphalocele, estimated to contain most of the small bowel which came through an umbilical ring 2.5 cm., or more, in diameter. The sac was estimated to be about 5 cm. in diameter and 5 cm. deep. The skin grew outward from the umbilical ring on the sac about 1.5 cm. The birth weight was 7 lb. 5 $\frac{1}{2}$ oz.



Fig. 5. Almost a front view of case 2



Fig. 6. A more oblique view of case 2

Under drop ether anesthesia, the defect was closed with a purse-string of silk (no. 5).

The child had an uneventful postnatal course, and when checked 19 days later, the cord was off and the base was healing firmly. The purse-string was removed at this time. At the age of 26 days the navel was completely healed and strong.

The child has developed normally. He does have an undescended testicle on the left side, but no other abnormality.

Figures 5 and 6 show the boy at the age of 23 months. The apparent bulging is solid tissue which may be due to the extension of skin outward on the sac at the time of birth.

SUMMARY

I believe the purse-string method can be used for many of the cases usually treated by open primary surgery and some cases that would otherwise require a two-stage operation. It does not permit inspection of the abdomen for other defects.

I have not had any experience with an omphalocele ruptured before or during delivery, but believe the purse-string method might be applicable in some of these cases.

The method seems to have the following advantages:

1. It is simple. It is almost as easy as applying

a cord clamp. It does not require an elaborate operating room set-up and can be done before the baby leaves the delivery room. A minimum of anesthesia is required for the short period of relaxation needed for forcing the sac contents into the abdominal cavity.

2. The abdominal cavity is not opened and because of this, has less opportunity for peritonitis.

3. There is less trauma to the intestines and probably less likelihood of adhesions to the abdominal wall.

4. There is no loss of tissue and the umbilical ring can support more tension than the cut edges of the peritoneum and fascia.

5. It does not seem to decrease the capacity of the abdominal cavity as much as the usual primary closure and may permit greater stretching of the abdominal wall.

6. It makes possible the normal evolution of the umbilical area that takes place in the days immediately following birth.

I have presented two cases treated by a new method, or at least one not commonly used. Although the results in these cases appear satisfactory, I realize that two cases are not enough to fully evaluate a method of treatment.

Acknowledgment. I wish to express my gratitude and appreciation to Robert L. Marsh, M.D., Pathologist at Parkview Episcopal Hospital and Pueblo Clinic, Pueblo, Colorado, for the use of microscopic sections shown in figures 1 and 2.

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FATAL HYPERPARATHYROID CRISIS ASSOCIATED WITH PANCREATITIS*

WILLIAM J. FINK, M.D., AND JAMES D. FINFROCK, M.D.

Fayetteville, Arkansas

Our purpose in presenting this paper is to call attention to the clinical picture of hyperparathyroid crisis or parathyroid intoxication which is difficult to diagnose in the absence of the classical signs of urinary tract or bone disease. A diagnosis of hyperparathyroidism is often overlooked when only gastrointestinal or non-specific complaints are present. As will be pointed out, clinical findings suggestive of peptic ulcer or pancreatitis may be the only clues indicating to the surgeon that he may be dealing with a case of hyperparathyroidism. Many surgeons are unaware of this.

When hyperparathyroidism is suspected, the possibility of hyperparathyroid crisis should also be anticipated. The main features of crisis are rapid onset of vomiting, constipation or obstipation, anorexia, weight loss, abdominal pain, fever, coma and collapse. Abdominal pain may simulate an acute abdominal disease.⁵ These symptoms are due to the hypercalcemia present. The syndrome may be devoid of skeletal findings but impairment of renal function is characteristic, even though renal calculi or a history of renal colic may be absent. Crisis should be suspected when, in the presence of a very high serum calcium (usually over 17 mg. per cent), there is evidence of uremia manifested by a rapidly rising blood urea nitrogen and an elevation of the serum phosphorus. Renal failure usually occurs followed by a shock like state, leading to rapid deterioration of the patient and ultimate death unless surgical removal of the suspected parathyroid adenoma is rapidly performed.

We have reviewed the literature concerning hyperparathyroid crisis as well as that relating to the association of hyperparathyroidism with pancreatitis and peptic ulcer. To our knowledge there have been approximately 56 cases of crisis

reported through 1959, of which 24 ended in death due to parathyroid intoxication. All but 3 of these 24 fatal cases were undiagnosed before death and the cause of death not proven until autopsy. Pancreatitis occurred in 34 per cent and peptic ulcer in 29 per cent (table 1).

We have noticed only brief mention of hyperparathyroid crisis in surgical literature dealing with hyperparathyroidism. In discussing this subject we have found that most surgeons are unaware of the entity of hyperparathyroid crisis. Our review of cases indicates that crisis may present such puzzling features that the diagnosis is often overlooked.¹³ As recently as March 1959, an excellent review of hyperparathyroidism appeared in surgical print, yet parathyroid crisis with its predominance of gastrointestinal symptoms was not mentioned.¹² The association of pancreatitis and peptic ulcer with this disease was also not emphasized.

In medical literature, however, there have been several excellent articles dealing primarily with crisis, stressing the importance of gastrointestinal complaints as presenting symptoms and reminding the medical profession that many of these patients may have no evidence of bone or renal pathology. St. Goar³⁷ succinctly stated, "Unexplained episodes of nausea and vomiting, unexplained anorexia and weight loss, peptic ulcers which do not respond to the usual therapy and a variety of unexplained abdominal pains should all lead to a consideration of hyperparathyroidism as a possible diagnosis. Hyperparathyroidism which is popularly thought of by medical men as a 'disease of stones and bones' might be recognized earlier and more frequently if it were regarded as a 'disease of stones, bones and abdominal groans'." With this statement we heartily agree.

The following case will illustrate some of the difficulties in diagnosing the syndrome of hyperparathyroid crisis. This patient presented signs and symptoms initially of intestinal obstruction and possible peptic ulcer but was soon found to also have pancreatitis. Although the correct

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diagnosis of hyperparathyroid crisis was made prior to death and a surgical attempt made to remove the parathyroid tumor, he expired because of the time lag between correct diagnosis and surgery.

CASE REPORT

A 60-year-old white man was admitted to the Fayetteville, Arkansas, Veterans Administration Hospital on February 10, 1958, with complaints of abdominal distention, cramping pain, vomiting and obstipation of 48 hours' duration. He had taken 10 enemas with no relief. Chronic constipation had been present for years. In 1945 he had an episode of abdominal pain, severe constipation and vomiting and his appendix was removed at a private hospital. In 1950 he was hospitalized because of melena and was given 2 blood transfusions for a bleeding duodenal ulcer. In 1953 and in 1956 he received hospital treatment for ulcer symptoms of pain, nausea and vomiting. In 1957 at a California hospital a gastric resection was contemplated because of pyloric obstruction but was postponed because of "heart trouble".

Examination revealed a well nourished but acutely ill man. His blood pressure was 150/90; pulse, 146. Heart and lungs were normal. The abdomen was diffusely distended. There was tenderness in the epigastrium and left upper quadrant. Peristalsis was hyperactive with occasional rushes. There was mild generalized abdominal rigidity. A 4-in. right rectus scar was noted. Remainder of examination was negative.

Initial laboratory studies revealed white blood count of 27,650 with 90 per cent neutrophils; hemoglobin, 16 grams; and hematocrit, 47 per cent. Urinalysis showed 1+ albumin, coarse granular casts and a few white blood cells per high-power field. Chest x-ray was negative. Abdominal x-rays showed no evidence of intestinal obstruction, although this was the initial clinical diagnosis. Because of the history of peptic ulcer a gastrointestinal series was performed to see if the pylorus was obstructed. No pyloric obstruction was found but what was interpreted as a giant duodenal ulcer was seen in the first portion of the duodenum.

Gastric suction was started plus intravenous fluids. He felt improved, but continued to complain of abdominal pain and tenderness. On the 3rd day he passed gas per rectum and oral feedings were started. The white blood count was still elevated to 23,000 with 86 per cent neutrophils. A serum amylase at this time was 173 units (normal 60 to 160 units). During the first 5 days his temperature averaged 100°. A large daily urine output was noted. On the evening of the 5th day mental

TABLE 1

Collected cases of hyperparathyroid crisis

Total cases	56
Fatal cases	24
Survived	32
Mortality rate	43%
Associated pancreatitis	34%
Associated peptic ulcer	29%

confusion was noted for the first time. His white blood count rose to 33,000 and pulse and temperature began rising. On the 6th day a serum calcium was reported as 20 mg. per cent and serum phosphorus was 4.9 mg. per cent. These tests were performed routinely as part of our screening of all peptic ulcer patients for possible hyperparathyroidism, although this diagnosis was not suspected when these were ordered.

We were surprised at the high calcium and elevated phosphorus level, the latter certainly not typical of classical hyperparathyroid disease. A laboratory error was thus suspected at this time. His mental confusion increased and he appeared much worse. He was transfused, oral feedings were stopped and intravenous feedings were restarted. On the 7th day a repeat serum calcium was still elevated to 17.9 mg. per cent and phosphorus 5.3 mg. per cent. The patient was now in acidosis with a blood CO₂ of 16.5 mEq. per L. Blood urea nitrogen was reported as 77 mg. per cent. His urine output began decreasing and the blood pressure dropping. His serum amylase rose slightly to 244 units.

It was at this time that hyperparathyroid crisis was diagnosed. We were somewhat reluctant to operate, however, because of his very desperate condition. The patient was started on cortisone, taken to surgery and the neck explored. Two nodules, the larger 1 cm. centimeter in size, were removed from the neck. During surgery his blood pressure was maintained with continuous intravenous Levophed. He expired 1 hour later with acute pulmonary edema. The nodules which had been removed proved to be adenomas of the thyroid and contained no parathyroid tissue.

At postmortem examination a large parathyroid adenoma, posterior to the esophagus in the posterior-superior mediastinum, was found overlying the vertebral column. The adenoma measured 5½ by 3½ by 3 cm. in size, was light brown in color and contained several green-blue cystic areas (fig. 1). Both lungs were firm and wet showing acute pulmonary edema. The pancreas showed multiple soft, yellow-white plaques on the surface. Pancreatic ducts were carefully dissected and showed no evidence of obstruction or calculi. The duode-

num was negative except for a pseudodiverticulum. Both kidneys appeared normal and contained no gross renal calculi.

Final pathologic diagnoses were: chief cell parathyroid adenoma with terminal hyperparathyroid crisis (fig. 2), subacute pancreatitis, microscopic calcification of the kidney tubules and pulmonary edema.

COMMENT

The case presented is typical of hyperparathyroid crisis ending in death. Like many others we were not certain of the diagnosis and delayed surgery until the patient was moribund. Our experience is almost identical with the experience of others dealing with crisis in which no diagnostic

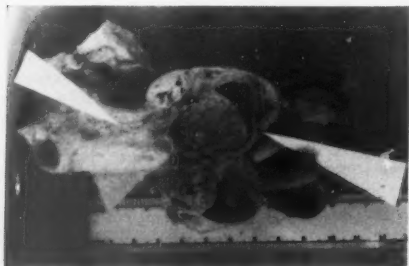


FIG. 1. Photograph illustrating parathyroid adenoma. Right arrow points to tumor which is cut in half. Left arrow indicates trachea.

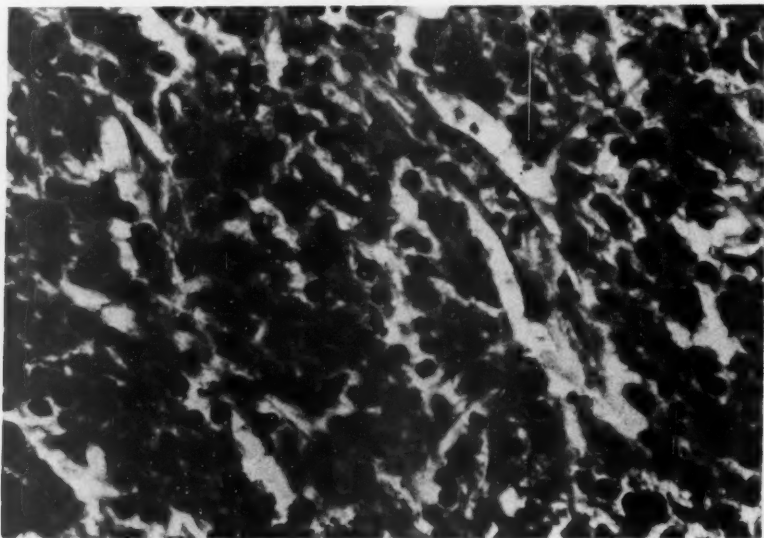


FIG. 2. High power ($\times 475$) photomicrograph showing chief-cell parathyroid adenoma

clues of osseous changes or renal calculi are present. The large parathyroid adenoma was undiscovered at surgery because of its location behind the esophagus in the posterior-superior mediastinum. It may be pointed out that in a series of 60 cases of parathyroid adenoma, 5 were found in the posterior-superior mediastinum.⁷ The correct antemortem diagnosis was made only because a serum calcium was ordered. The high phosphorus, in our experience, did not fit with the usual finding of a low phosphorus which occurs in the typical classical case of chronic hyperparathyroidism. We did not know then that the phosphorus rises as crisis occurs and renal failure develops. We were misled primarily by a clinical picture simulating intestinal obstruction at first, then peptic ulcer and later subsiding pancreatitis.

DISCUSSION

Lowenberg and Ginsburg²⁷ in 1932 described the clinical picture of hypercalcemia in a 5-year-old boy given large doses of Parathormone by mistake, who then developed nausea, vomiting, weakness, fever, depression and abdominal distress. In 1939, Hanes¹⁶ reported the first case of death from parathyroid poisoning observed clinically in man. Oliver³⁰ reported 2 cases of fatal crisis exhibiting mainly gastrointestinal

complaints. Smith and Cooke³⁶ added two similar cases and Rogers³⁴ reported 2 patients dying in hyperparathyroid crisis unrecognized during life, both with active peptic ulcers and neither having bone or renal disease.

James and Richards³⁰ reviewed the literature and in 1956 collected 14 cases of crisis and added one of their own successfully operated. Of these 15 cases 11 were fatal. Hewson¹⁷ added 4 additional fatal cases and reported on a total of 23 cases of hyperparathyroid crisis. Additional cases have been reported by others.^{3, 19, 22, 24, 25, 32, 37-39, 40, 41}

Of the 56 cases of hyperparathyroid crisis collected, 24 were fatal. The mortality rate was therefore 43 per cent. Of these 24 cases, 21 were undiagnosed before death.

Unfortunately, hyperparathyroid crisis rarely is identified. Goldman¹⁵ discussed the changing diagnostic criteria for hyperparathyroidism stating that only 2 of his 23 cases had bone disease. Jarvis and co-workers²¹ saw 5 out of 9 patients without evidence of symptomatic osseous changes or renal stones, who had esoteric complaints considered to be functional.

Protean clinical manifestations have so obscured most recorded cases of true crisis that there is an unfortunate time lag between onset of symptoms and ultimate diagnosis.¹⁹ Farrell¹¹ has discussed physiologic considerations in the diagnosis and management of hyperparathyroidism relating the symptoms to hypercalcemia. In addition to the predominance of gastrointestinal complaints seen in hypercalcemia, there may be other vague symptoms of hypercalcemia such as weakness, cardiac arrhythmias, lassitude, leg pains and mental disturbances. These symptoms are so common in the population that dependence on them in diagnosing hyperparathyroid crisis early in the illness is often unrewarding.⁸

We feel that the primary diagnostic clues to the acute crisis of hyperparathyroidism are those of gastrointestinal complaints, peptic ulcer symptoms, pancreatitis, polyuria and later oliguria leading to renal failure, muscular weakness³⁵ and collapse, and personality changes (table 2).

Pancreatitis as a diagnostic signpost of hyperparathyroidism was recently pointed out by Cope and others⁸ and Hoar.¹⁸ Pancreatitis may be caused by excessive Parathormone which produces focal pancreatic necrosis or may arise

TABLE 2

Clinical clues to hyperparathyroid crisis

1. Abdominal pain
2. Anorexia, vomiting
3. Fever, weight loss
4. Constipation or obstipation
5. Peptic ulcer
6. Pancreatitis
7. Cardiac arrhythmias
8. Renal failure
9. Polyuria or (late) oliguria
10. Personality changes

because of deposition of calcium carbonate or phosphate calculi causing pancreatic duct obstruction. Coffey and colleagues⁶ have suggested that all cases of calcific pancreatitis should be screened for evidence of hyperparathyroidism. It is interesting that the elevated serum calcium in this disease may be reduced in complicating pancreatitis, thus rendering the diagnosis of hyperparathyroidism difficult. Conversely, normal calcium levels in this situation may mask pancreatitis and lull the physician into a false sense of security regarding the gravity of the pancreatic disease. Our case had calcium levels up to 20 mg. per cent. One wonders how high the serum calcium level might have been had there been no associated pancreatitis! Of the 56 cases collected by us, we have found that 19, or 34 per cent, had either pancreatitis or pancreatic calculi.

One might logically ask whether the predominance of gastrointestinal complaints in hyperparathyroid crisis could not be principally due to an associated pancreatitis. In the first place, vomiting, abdominal pain, anorexia and constipation occur in any type of severe hypercalcemia. Secondly, 66 per cent of the cases of crisis we have collected had no evidence of pancreatitis and yet all were characterized by the above gastrointestinal symptoms.

Peptic ulcer as a complication of hyperparathyroidism has been emphasized by St. Goar,³⁷ Jarvis and others,²¹ Rogers³⁴ and Anlyan.² The relation of peptic ulcer to this disease is not clear. Kirsner²² suggested that multiple endocrine influences of the pituitary and adrenal gland may play a significant role. We found that 16, or 29 per cent of the 56 cases of hyperparathyroid crisis reported here gave a definite history of peptic ulcer. It may well be that those ulcer

patients who cannot tolerate milk and alkali therapy and become worse on this regime have hyperparathyroidism. Berne³ stated that duodenal ulcer is 11 times more frequent in hyperparathyroidism than in the normal population.

Classical chronic hyperparathyroidism is confirmed by laboratory studies which show a low phosphorus, an elevated calcium, and an increased excretion of calcium and phosphorus. Most patients diagnosed today, however, do not fit into this classical pattern. Goldman and co-workers¹⁵ found that 60 per cent of his patients with proven hyperparathyroidism had serum phosphorus levels in the range of normal. With impaired renal function, phosphorus levels may be normal or elevated.

The tubular phosphate reabsorption test (TPR) has become a valuable screening test for hyperparathyroidism.²⁵ It is known that Parathormone inhibits the reabsorption of filtered phosphate, so that in hyperparathyroidism a diagnostic positive TPR shows a reabsorption of 78 per cent phosphate or less. Normally the renal tubules reabsorb 80 to 90 per cent of phosphate filtered through the glomeruli. Goldman and colleagues¹⁵ found a lowered TPR in 21 of 22 proven cases. The TPR test is not specific, however, for it may be low also in osteomalacia, sarcoidosis, multiple myeloma and uremia. After the removal of an adenoma, a rising TPR is welcome evidence of a successful operation. Farrell¹¹ stated that he would be most reluctant to recommend surgical exploration in the face of a normal or elevated TPR.

Hypercalcemia is the most important biochemical change in hyperparathyroidism and is caused by the mobilization of calcium from the bones. It should be remembered that the total serum calcium is present in 3 forms—ionized, protein bound and complexed with organic acids.^{9, 10} The rise in calcium in hyperparathyroidism is primarily in the ionized fraction. This rise could be masked, if there were, at the same time, a fall in one of the other fractions, as for example, in a patient with a low serum protein. Lloyd and Rose²⁶ found the ionized-calcium fraction always raised in patients with functioning parathyroid adenomas, and after the adenoma was removed the level fell. They concluded that the ability of the plasma proteins to bind calcium is reduced in this disease.

Unfortunately, at the time the case presented

in this paper was being treated, we did not have the laboratory advantages of TPR and ionized-calcium studies.

Bradlow and Segel⁵ described electrocardiographic changes in hyperparathyroidism. Shortening of the QT interval and an almost absent ST segment is said to be characteristic of hypercalcemia. In their case of crisis the electrocardiographic changes reverted to normal after removal of a parathyroid adenoma.

Dent and co-workers⁹ has shown that serum calcium levels in primary hyperparathyroidism are not lowered after the administration of cortisone. Since other diseases producing hypercalcemia will show a response to cortisone with a drop in the calcium level, the cortisone test is of value in arriving at a decision for or against surgical exploration. Farrell¹¹ has affirmed the value of this cortisone test.

Laboratory aids in the diagnosis of hyperparathyroidism with crisis may then be summarized as follows: A total serum calcium usually over 17 mg. per cent, a high ionized-calcium (if this test is available), a normal or high serum phosphorus, uremia as evidenced by a rising blood urea nitrogen, an elevated amylase if pancreatitis is present, a low tubular phosphate reabsorption test, characteristic electrocardiographic changes and no lowering of serum calcium after cortisone administration (table 3).

The cause of death in parathyroid crisis is usually uremia because renal damage is often too far advanced before the diagnosis is finally recognized. Failing renal function, rising calcium, elevation of urea nitrogen and a rising phosphorus are the danger signals of crisis.¹ This terminal clinical picture is noted in practically all of the fatal cases reported. In addition to uremia, death may also be contributed to by actual cardiac poisoning¹⁷ or adrenal insufficiency.²⁰

It is possible that chemical chelation with ethylene-diamine-tetraacetic acid, Endrate (Abbott), may be used to correct hypercalcemic crisis. This chemical compound unites with the cation calcium, to form a stable ring structure or chelate wherein calcium ceases to act as a free ion. James and Richards²⁰ have mentioned the use of this compound. Clinical trials have been too few, however, to clinically substantiate the usefulness of this compound in true hyperparathyroidism.

TABLE 3

Laboratory aids in diagnosis of crisis

1. Calcium over 17 mg. %
2. Normal or high phosphorus
3. High blood urea nitrogen
4. Elevated amylase
5. Low tubular phosphate reabsorption
6. EKG changes
7. No lowering of calcium after cortisone
8. X-ray evidence of renal calculi, or pancreatic calculi or peptic ulcer
9. Osseous changes on x-ray

Prompt surgical removal of the offending parathyroid adenoma is the treatment of choice. Some 10 per cent of cases with hyperplasia would require subtotal parathyroid resection.⁴ The main goal in treatment, however, should be to make the diagnosis before obvious and serious complications develop and cause death.^{29,33}

CONCLUSION

1. The case presented, plus those collected from the literature, makes a total of 56 patients reported with acute hyperparathyroid crisis. Of these patients 24 died—a mortality rate of 43 per cent. In almost all fatal cases the diagnosis was unsuspected before postmortem examination.

2. Attention is called to the puzzling clinical picture and difficulties in diagnosing hyperparathyroid crisis. Crisis is characterized by acute gastrointestinal complaints and is often associated with pancreatitis (34 per cent) and with peptic ulcer (29 per cent). When bone or renal disease is absent the diagnosis may be overlooked.

3. The main features of crisis are due to hypercalcemia. These are vomiting, constipation, anorexia, weight loss, abdominal pain, fever and collapse. Crisis should be suspected when, in the presence of a serum calcium of 17 mg. per cent or over, the serum phosphorus also rises and uremia then develops leading to renal failure and death.

4. Clinical and laboratory aids in diagnosis are discussed which should assist the clinician in arriving at the correct diagnosis so that early surgical neck exploration can be instituted before terminal complications develop.

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TRAUMATIC BRONCHOBILIARY FISTULAE

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Persistent bronchobiliary fistulae are rarely seen as a result of, or as a complication following trauma. Their management differs from that of bronchobiliary fistulae from other causes and, therefore deserves special consideration. Since 1879, six cases have been reported in the literature; a seventh case is added (table 1).

CASE REPORTS

*Case 1.*¹ A 25-year-old man was kicked by a horse on January 28, 1897. The blow produced a contusion of the right 5th, 6th, 7th and 8th rib cartilages without fracture. Severe pain was felt in the chest and right shoulder. Four hours later the abdomen was very much distended. The man expectorated mucous tinged with blood. Four days later, a diagnosis of pneumonia was made and after 1 week there was a right pleural effusion.

On February 15, the patient coughed up bile. The quantity was small at first and came only after severe attacks of coughing. Subsequently, it came in large quantities with less effort. Empyema drainage was instituted on February 16. For some time bile stained fluid drained. No jaundice was present. Expectoration of the bile increased after the first operation. On March 2nd, at a second operation, portions of the 6th and 7th ribs were removed, and a second drainage tube was introduced directly below the first. After the second operation the stools became colorless. The patient was seen again on April 8. There was dullness below the 9th rib on the right side of the chest. Both tubes were still draining small amounts of bile and mucous. Over a long period of time, the patient improved and the fistula as well as the emphyema drainage closed. The stools returned to normal color and the patient recovered.

*Case 2.*² On November 18, 1908, a 22-year-old soldier shot himself in the right chest in a suicidal attempt. When seen approximately 1 hour later he was in shock. The wound of entrance was in the right mammary line at the level of the 5th rib. The point of exit was in the midscapular line at the 9th interspace. Both openings were stopped with gauze tampons. Percussion and auscultation

revealed a decrease in the breath sounds and resonance over the lower right chest. The liver was felt slightly below the costal margin. The heart had a slight shift to the left. Dark blood and air bubbles continued to be seen in the wounds. On November 25th, the bandage was soaked with bile. Bile drainage became profuse over the next few days. On November 29 the patient coughed up a large amount of yellow-green, bitter tasting sputum mixed with pus. Bile continued to drain through the wounds. This continued for 22 days. On December 22, the patient was taken to the operating room and 12 cm. pieces of the 5th and 6th ribs from the wound entrance toward the midaxillary line were removed. Adhesions were found between the lung and the diaphragm. A stronger obstacle, which looked like an adhesion but was about the size of a finger, was felt between the diaphragm and the lung. This fistula was cut and both ends tied off. The emphyema cavity was filled with gauze and the wound was left open for drainage of the emphyema. After the operation there was a very small amount of drainage. The patient ceased coughing up bile and the bandages were no longer soaked with it. Within 3 weeks the wound had closed and the emphyema had completely healed. Recovery was complete and the man returned to duty.

*Case 3.*³ A case of fistula between the biliary tree and the bronchus came under the care of Capt. St. J. D. Buxton. A septic hemothorax of the right side was caused by a schrapnel ball which traversed both sides of the chest. After being wounded the patient began to expectorate sputum mixed with yellow bile, but the precise date of this could not be ascertained because of the physical obsession which made all the patient's statements on questions unreliable. On the 26th day after the wounding, the empyema on the right side was drained. It contained streptococci and staphylococci. Frothy sputum with patches of bright yellow bile and, occasionally, with fleshy masses of necrotic liver tissue, proved by microscopic section, continued to be coughed up. Lt. Col. H. P. Hawkins reported from England that the expectoration of bile ceased on the 10th week. The empyema sinus was practically closed during the 14th week and the patient was rapidly becoming fit again.

*Case 4.*⁴ A 12-year-old boy fell to the bottom of

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TABLE 1
Case reports

No.	Date	Age	Sex	Cause
1	1897	25	M	Kicked by horse
2	1907	22	M	Suicide attempt
3	1915	24	M	Shrapnel wound
4	1929	12	M	Accidental stab wound
5	1944	28	M	Gunshot wound
6	1944	25	M	Gunshot wound
7	1953	31	M	Gunshot wound

a dry well on October 5, 1929. He received a penetrating wound of the right upper posterior chest and a wound of the right groin, extending into the abdominal wall. On the following day the patient was admitted to the hospital. He was cyanotic; had a weak pulse of 130; temperature, 102°; and was in a desperate condition. The right anterior chest showed bronchial breathing, a few scattered rales and impaired percussion. The left side was normal. The abdomen was somewhat tender with moderate general rigidity. There was marked tenderness over the liver. The patient had a severe leukocytosis with 90 per cent polymorphonuclear leukocytes. On the following night the patient vomited bile and small clots of blood. On the next day the patient was somewhat improved but continued to vomit large amounts of bile and blood clots. An x-ray film taken that day showed a pleural effusion with a fracture of the 8th rib. Fluoroscopy of the chest revealed a fluid level with no diaphragmatic excursions on the right. On October 10 the patient coughed up a small blood clot. This continued over the following 8 days.

On October 18, the patient noted for the first time that his sputum had a very bitter taste. It was yellow in color. On the following day large amounts of bile and blood were expectorated. The sputum had a very offensive odor. His condition appeared to be growing worse.

On October 22, after aspirating the chest cavity, a 3-in. piece of the posterior right 9th rib was removed and an empyema drained. At this time a projection about the size of a thumb was noted extending between the diaphragm and the lower portion of the collapsed right lung. A needle inserted into this sinus obtained bile. An opening was made into the fistulous tract and a large tube was put directly into the tract and a second large rubber drain tube was put into the pleural cavity, both being brought out through the chest wall. The patient's condition improved after surgery. The coughing of bile decreased. In 5 days the

drainage of bile from the thoracotomy tubes had ceased. On October 30th an x-ray showed residual empyema cavity. On November 4th, the empyema cavity was treated with Dakin's solution which continued for 15 days. Two weeks later the empyema was healed. Follow-up showed complete clearing of the chest.

*Case 5.*⁶ A 28-year-old soldier was injured by a rifle bullet entering the right anterior chest wall medial to the nipple at the level of the 5th rib and emerging posteriorly in the midscapular line over the 10th rib. A thoracotomy was performed 10 hours later. Portions of the 10th and 11th ribs were resected and the pleural cavity explored. Lacerations of the right lower pulmonary lobe and diaphragm were sutured. The chest was closed tightly with a catheter drainage. The patient spit up bloody sputum for 3 days. Three days after the thoracotomy there was a residual hemopneumothorax. Nine days after being wounded the patient first noticed a bitter tasting sputum, slight in amount at first, but increasing daily thereafter. Expectoration of a yellow, bitter sputum continued. The thoracotomy wound was unhealed. X-ray films revealed fluid in the right pleural cavity with a 20 per cent collapse of the right lung and elevation of the right diaphragm. The expectoration of bile stained sputum continued. On August 4, 1944, 25 days after the wounding, under local anesthesia, a phrenic nerve crush was carried out. Four days later the patient coughed up 500 cc. of blood and 900 cc. the following day.

On August 10, a thoracotomy was done through the bed of the removed 9th rib. The lung was freed and the empyema cavity was drained. Through a defect in the diaphragm a large sub-diaphragmatic space filled with blood clots was found. After the clots were removed an alarming hemorrhage from the liver bed occurred. A fistula was noted in the lower lobe of the lung. By wedge resection the fistula was removed and the bronchus was repaired. The thoracotomy wound was closed at both ends, leaving the center open for access to the liver bed through the diaphragm. This was packed. On August 16 a hemorrhage from the liver bed occurred. On August 21 the packing was removed. The following day a hemorrhage occurred from the liver. The liver was repacked. The packing was gradually extracted and the thoracotomy wound healed. On November 22 an x-ray showed a completely re-expanded right lung. The patient, upon recovery, was discharged from the hospital.

*Case 6.*⁶ On July 4, 1944, a 25-year-old pilot was wounded in the left arm by a bullet; later that day he was again wounded by a shell fragment which

entered the anterior, right chest at the level of the second rib in the midclavicular line. Examination revealed the fragment to have passed through the right lung and diaphragm and to be lodged in the liver. On the following day the patient was seen in an evacuation hospital, the wound was debrided and 600 cc. of blood aspirated from the pleural cavity. The patient's chest wound remained quiescent until 45 days after the wounding at which time he complained of pain in the upper abdominal quadrant. He had a temperature of 101.0°. At that time a fluid level was noted beneath the right diaphragm.

On August 22 the right anterior subphrenic space was entered and approximately 600 cc. of bile stained purulent material were evacuated. The subphrenic space was drained. On September 4, the temperature rose again and the patient coughed up 500 cc. of foul smelling, bile stained, purulent material.

On September 19, through a right rectus incision, the anterior subphrenic space was explored. A foreign body, measuring 2 by 1 cm. was removed from the substance of the liver and the space drained. In 3 weeks the cough and expectoration had stopped. The bronchobiliary fistula closed after persisting for about 30 days. On October 9 pleural fluid was noted. No aspiration was done. On October 11, the subphrenic space was again opened through a rectus incision. A moderate amount of pus was evacuated and a large catheter was left in place. Daily irrigations were carried out. By November 1, the patient was afebrile and had gained 15 pounds. He progressed to an uneventful recovery.

Case 7.¹ A 31-year-old corporal was wounded on May 5, 1953, by enemy smallarms fire. The bullet entered the lower right chest posteriorly, injuring the lower lobe of the lung, the diaphragm and the liver. On that same date a repair of the wound of the lower lobe, the right lung, laceration of the liver and of the diaphragm was done. The thoracotomy wound was closed primarily with underwater drainage and with a Penrose drain beneath the diaphragm draining the liver bed. Four days later the patient developed a hemothorax which persisted even though it was treated by a thoracotomy drainage tube and multiple aspirations. Eighteen days after the wounding the patient vomited a large amount of bright red blood. X-ray revealed air beneath the right diaphragm and fluid in the right chest. On June 1, 26 days after the wounding, the abdomen was explored because of a large mass in the right upper quadrant. This was diagnosed as an enlarged liver. The subdiaphragmatic space was not entered. Two days after the second operation the



FIG. 1. Lipiodol injected through a cutaneous fistula outlines a posterior emphysema cavity, an anterior subdiaphragmatic abscess and the tracheobronchial tree through a bronchobiliary fistula. Note that the tracheobronchial tree is normal after being bathed in bile for 30 days.

patient coughed up large clots of fresh blood. The hemorrhage occurred again the following day, and on June 10 and 11. The patient developed a pulmonary atelectasis. On July 18 the patient first coughed up bile stained sputum, and at the same time a cutaneous fistula opened at the upper end of the thoracoabdominal wound. Bile drained through this fistula. Subsequent examination revealed a bronchobiliary fistula with a subdiaphragmatic abscess and an emphysema. Bronchogram outlined the bronchobiliary fistula (fig. 1). Bronchoscopy and bronchograms revealed the tracheobronchial tree to be normal.

On August 17, 1953, the extrahepatic bile ducts were explored and the common duct drained. The fistula was outlined by Diodrast injected into the common duct. After this operation the bile fistula closed. On November 19, a pulmonary decortication, repair of the bronchial fistula, obliteration of the emphysema cavity, repair of the diaphragm and obliteration of a small subdiaphragmatic space were carried out. On December 20 a residual emphysema was drained. The patient then made an uneventful recovery and returned to duty.

INCIDENCE

In a review of the literature containing reports of 4072 casualties due to chest wounds occurring

in World War II and in the Korean campaign, including 1676 thoracoabdominal wounds, 3 cases of persistent bronchobiliary fistulae were reported.^{2,3} Two cases were reported from World War II by Guy and Oleck⁶ and one from the Korean conflict is reported in this paper.¹ The rarity is not due to lack of thoracoabdominal wounds, nor to the high immediate mortality. It is because of the fact that biliary pleural communication after trauma heals quite readily after proper treatment, if the biliary tract is normal. It rarely persists long enough for the formation of a true fistula. Persistent bronchobiliary fistulae due to disease are much more common than those due to trauma.¹

ETIOLOGY

These fistulae occur as a result of thoracoabdominal injury involving the right lung, diaphragm and liver. In 6 cases the wound was a penetrating type and in 1 a nonpenetrating wound. Five wounds were caused by fire arms, one resulted from being kicked by a horse and the other resulted from a fall. In each case the injury was primarily to the chest, but obvious injury occurred to the diaphragm and liver.

PATHOLOGY

Traumatic bronchobiliary fistulae differ from bronchobiliary fistulae due to other causes in several ways: (1) the biliary tract and bronchial tree are normal before injury; (2) biliary obstruction is not present; (3) the injury and onset are acute and may be associated with massive contamination, with tissue destruction and with severe bleeding.

The injury must be one that results in an open bronchus, lacerated diaphragm and open biliary radicals. After the injury, each of these cases developed a hemopneumothorax. One responded to aspiration of the pleural cavity,

and the other 6 had persistent hemopneumothorax that subsequently developed into empyema (table 2).

Subdiaphragmatic abscess developed in 3 cases and 2 bled severely. One of these cases had a foreign body in the liver. Two of these cases developed severe bleeding from the liver and each coughed up large quantities of blood. In each case the bleeding was nearly fatal. One case bled from the tracheobronchial tree with no evidence of subdiaphragmatic abscess. Two cases had bleeding from the gastrointestinal tract.

In each of the 7 cases, thoracoabdominal injury occurred resulting in a communication between the chest and abdominal cavity through a lacerated diaphragm; all developed fistulas. Four had an empyema only, 1 had only a subdiaphragmatic abscess and 2 had both.

The bronchial tree was examined in only 1 of these 7 cases. It was found to be normal. In a study of 66 cases of bronchobiliary fistulae from various causes, only 1 case of necrotizing pneumonia was found in the autopsy examinations that were reported.¹ In many cases a clinical diagnosis of bronchitis or pneumonia was made. Six cases of bronchiectasis were reported after autopsy or bronchogram.¹ Two cases of pneumonia were proved in these 66 cases.

Bile, in itself, is not injurious to the tracheobronchial tree (fig. 1). If infection or obstruction occur within the biliary tract or the tracheobronchial tree, bronchitis, bronchiectasis, pneumonia, or lung abscess may occur. It is interesting to note that cases with long standing biliary obstruction and bronchial fistula rarely develop permanent injury to the tracheobronchial tree unless gross infection is present.

Persistent biliary obstruction was not seen in these cases of fistula due to trauma, and the biliary tree was apparently normal in all, although it was explored in only one case. Transient obstruction due to bleeding into the biliary tree may occur.

TABLE 2
Pathology in 7 reported cases

Hemopneumothorax.....	7
Empyema.....	6
Subdiaphragmatic abscess.....	3
Gastrointestinal bleeding.....	2
Bleeding from liver.....	2
Bleeding from lung.....	1
Foreign body in liver.....	1

SYMPTOMS AND DIAGNOSIS

The diagnosis of traumatic bronchobiliary fistula is made simply by finding bile in the sputum. The etiology is obvious. Symptoms are those of persistent hemopneumothorax, empyema and subdiaphragmatic abscess. There may be shortness of breath, severe productive cough,

fever, night sweats, occasionally cyanosis, weight loss and a gradual septic, downhill course. Bleeding from the tracheobronchial tree or gastrointestinal tract occurred in 3 cases. Jaundice is rare, occurring in only 1 case.

The actual coughing up of bile occurred on an average of 31 days after the injury. In 1 case it occurred 9 days after injury and in another case it failed to appear until the 74th day. In 1 case the exact time is not known. The diagnosis of an empyema is readily made by x-ray and thoracentesis. A fluid level was seen on x-ray beneath the right diaphragm in each case that developed a subdiaphragmatic abscess.

TREATMENT

The prevention of bronchobiliary fistulae lies in the proper treatment of the acute injury. The lung injury must be properly repaired to prevent hemorrhage and bronchial fistula. The lung must be promptly expanded to fill the pleural space. The pleural space must be drained underwater. The diaphragm should be completely repaired to act as a barrier to such a fistula. Repair of the liver must be carried out, the bleeding controlled, foreign bodies removed and necrotic tissue removed. The subdiaphragmatic space should be properly drained through the flank or belly wall. It is understandable that in severe injury with massive tissue destruction all of these things cannot always be accomplished.

In treatment of the established fistula, drainage of the infected spaces is mandatory. This was required in each case. Empyema drainage alone was effective in 2 cases. In 1 case, drainage of the subdiaphragmatic abscess was all that was necessary. In 1 case, the fistula was tied off, and

TABLE 3

Treatment

Surgical Procedures	No. of Cases
Drainage of empyema.....	6
Drainage of subdiaphragmatic space...	3
Fistula tied only.....	1
Fistula drained.....	1
Fistula divided and closed.....	2
Liver packed.....	1
Biliary tract drained.....	1
Decortication.....	1
Phrenic crush.....	1

TABLE 4

Treatment	Case No.						
	1	2	3	4	5	6	7
Drainage of empyema..	x	x	x	x	x		x
Drainage of subdiaphragmatic space.....					x	x	x
Fistula tied.....		x					
Fistula drained.....				x			
Bronchial fistula close operatively.....					x		x
Liver packed.....					x		
Biliary tract drained...							x
Decortication.....							x
Phrenic crush.....					x		

x = designates in which case each procedure was used.

in another it was drained. These were successful only because there was no biliary obstruction. In cases of biliary obstruction such a procedure will fail. If one suspects biliary disease or obstruction, an exploration and drainage of the extrahepatic biliary tract should be carried out. This is not usually necessary in fistulae caused by trauma. It was carried out in one of the reported cases and was effective in closing the biliary fistula (tables 3, 4).

In cases with both an empyema and subdiaphragmatic abscess, the drainage of both is required. Two such cases are reported. Foreign bodies in either the pleural or subdiaphragmatic space must be removed. Their presence promotes infection. Such was true in 1 case. Severe bleeding from the liver occurred in 3 cases. In 1 case exteriorization and packing of the liver were necessary. Operative closure is necessary in persistent bronchial fistulae. Such a closure was necessary in 2 cases. Phrenic crush was carried out in 1 case without benefit to the patient. Pulmonary decortication may be necessary in the treatment of empyema. This was carried out in 1 case. Secondary repair of the diaphragm should be carried out if a defect is present (tables 3, 4).

In summary, every effort must be made to prevent this complication by proper treatment of the acutely injured. In the established fistula, drainage of the infected spaces is most important. Tying off of the fistula is effective but not usually necessary. If biliary obstruction is suspected, the biliary tract should be explored and drained.

Severe bleeding from the liver may require exteriorization and packing. Persistent bronchial fistula will require operative closure or pulmonary resection.

PROGNOSIS

The prognosis is good after proper treatment. All of the cases survived and recovered with no residual fistula following surgery.

SUMMARY

1. Bronchobiliary fistulae as a result, or complication, of thoracoabdominal injury are rare.
2. Seven previously reported cases are reviewed and discussed.
3. The symptoms and signs associated with traumatic fistulas differ from other bronchobiliary fistula in several ways. These are discussed.
4. Because of the lack of biliary obstruction the principles of treatment of these cases differ from bronchobiliary fistulae from other causes. The principles of treatment are discussed.
5. The presence of bile in the tracheobronchial

tree does not in itself cause severe or permanent damage to the tracheobronchial tree. Secondly, obstruction or infection may cause damage.

6. All the patients survived without fistulae, following surgery.

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THE ASYMPTOMATIC RESIDUAL AIR SPACE AFTER PARTIAL PULMONARY RESECTION*

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For more than five years there has been considerable curiosity on the part of chest physicians as to the significance of the nonsymptomatic residual air space which remains after segmental resection or lobectomy. Gradually, there seems to have been an assumption that most of these air caps have not too much significance, and that they disappear from the chest film in a matter of months.

It was suggested by one of us (J. G.) that bronchography might prove useful in evaluating these cases as reported in a discussion in 1954.¹

Over the past few years we have been evaluating some of these spaces by means of bronchograms and, on occasion, operative intervention. Our experience with cases gleaned from 31 lobectomies and 76 segmental resections in that period is illustrated by the following case reports.

CASE REPORTS

Case 1. R. G., 41,378. This 33-year-old man contracted tuberculosis in February 1953. Following chemotherapy and bed rest, 12 months after initiation of therapy, the contracted right upper lobe was removed. Because of dense pleural plaques, complete expansion of the remaining lung was not secured. Postoperatively, he had an unexpanded space which was completely asymptomatic. Bronchography, however, demonstrated that there was free communication between a bronchus and the space. Thoracoplasty, to obliterate the space, was done following this demonstration. At the present time the patient is well, with consistently negative cultures. Bronchogram now shows no communication.

This patient represents a case of wide open bronchopleural fistula into an asymptomatic postresection air space. A satisfactory result was obtained by thoracoplasty.

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* From the Veterans Administration Hospital, Albuquerque, New Mexico. Bronchograms in this study were performed by Dr. Bernard Lowenstein.

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Case 2. P. P. L., 42,442. This 27-year-old taxi driver was discovered to have tuberculosis in March 1953. He was treated with bed rest and antimicrobial therapy. The bilateral cavitary tuberculosis stabilized, with residuals, and in March 1954, a left upper lobectomy, combined with subsegmental resection of the left lower lobe, was performed. A residual air cap on the left remained, but resection on the right was accomplished in June 1954. The patient was completely asymptomatic after his surgery, with no cough, sputum or fever. Gastric smears and cultures, however, showed occasional positives up to the end of 1954.

Bronchograms, which were done in June 1955 showed bronchial distortion, but no communication with the left sided air space. Tomograms, however, done in March 1955, showed clearly an area of communication between a bronchus and the left apical air space. A thoracoplasty was advised, but was not accepted by the patient and he left the hospital against advice. This man was seen in April 1956 at another hospital. At that time he was asymptomatic, but the cyst-like space was still present, by x-ray.

This patient's air containing space continues as evidence of a bronchopleural fistula for over two years.

Case 3. S. B. C., 44,009. This 26-year-old patient was discharged from the Army to our hospital in January 1954, with a diagnosis of tuberculosis, proved by positive sputum. Examination showed a residual lesion with cavitation in the left upper lobe. After 9 months of antimicrobial therapy his sputum became negative to culture. In March 1954, resection of the apical posterior segment of the left upper lobe was done. The patient had an essentially uncomplicated recovery, but the residual lung did not expand as fully as was expected. This space was asymptomatic, but bronchography now showed a communication into it. Since the space produced no symptoms, a policy of continued observation was then adopted. Eight months after operation the space was essentially obliterated, on routine x-ray film. Bronchography at this time, however, showed a residual pocket, and for this reason thoracoplasty was done in January 1955. Bronchogram done 8 months after thoracoplasty showed no pocket. The patient had never been positive to culture in this institution.

This patient demonstrates that apparent obliteration of the space on posterior anterior roentgenogram is not necessarily proof of disappearance of the residual air space with communicating bronchus.

Case 4. This case is similar to case 1.

Case 5. J. C. P., 40,658. This 37-year-old man had a diagnosis of pulmonary tuberculosis made in June 1943. He had a year's hospitalization until 1944, during which time a pneumothorax on the left was instituted and was continued until 1948. In January 1953 the patient was found to have persistent positive sputum with cough. He was placed on a regimen of bed rest and antimicrobials. After 8 months of this therapy, sputum smears and cultures were still positive. He then had resection of the anterior and apical posterior segments of the left upper lobe, a decortication and a 3-rib thoracoplasty. The post-resection space persisted asymptotically for several months. The patient recovered well from his operation, but continued to show occasional positive sputums. The organisms showed complete antibiotic resistance.

A bronchogram, which was done 10 months following operation showed no empyema pocket that filled with dye, but a dilated bronchus leading to an air pocket could be seen. Drugs were changed to isoniazid INH, and pyrazinamide, but positive sputums persisted. This man was followed for another 9 months and he continued to have occasional positive sputum, so in June 1955 he was reoperated upon. The empyema cavity measured only about 2 cm. in diameter, but was positive on

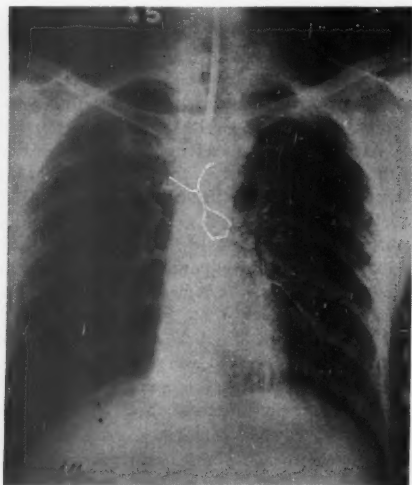


FIG. 1

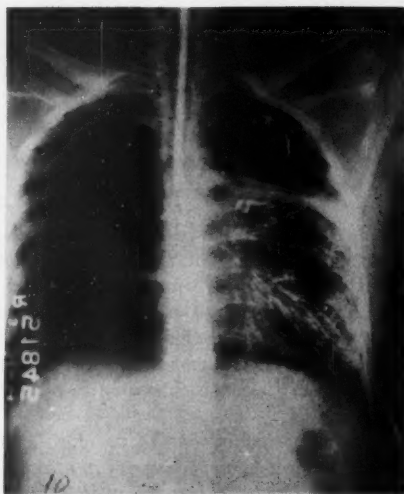


FIG. 2



FIG. 3

smear and culture. It communicated directly with a short segment of upper lobe bronchus. The thoracoplasty was revised by the removal of one more rib, and resection of the scapula. The patient did extremely well after operation, and has been negative on smear and culture ever since this last procedure.

This patient continued for 2 years after resection completely asymptomatic except for positive



FIG. 4

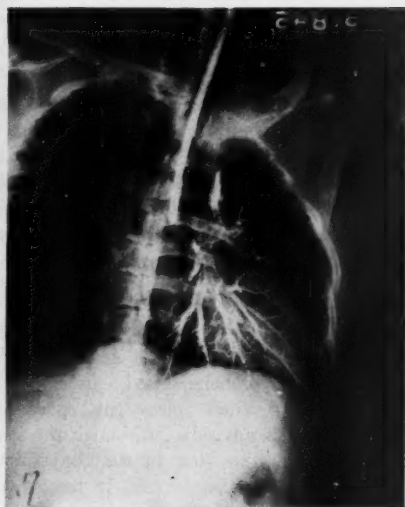


FIG. 5

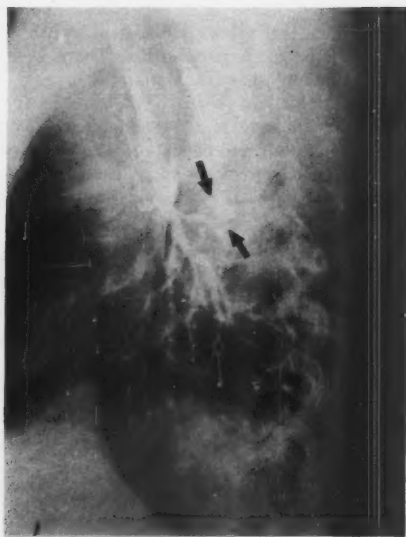


FIG. 6

gastric cultures obtained on routine follow-up examination. Operation proved that the preoperative bronchogram correctly predicted a communicating empyema pocket.

Case 6. P. R. B., 50,793. This 44-year-old man had had severe bilateral tuberculosis for which the following operations had been done in other hospitals: a left thoracoplasty in 1949; a left upper

lobectomy and removal of the superior segment of the left lower lobe in 1951; and a drainage of an empyema of the left chest following his resection, again in 1951. Apparently the drainage of the empyema cavity was successful because of all his symptoms disappeared. He remained clinically well, but had persistent positive gastric cultures

on follow-up examination. For this reason he was studied in 1955 and 1956 at this hospital.

A bronchogram clearly showed a pocket leading from the amputated bronchus of the superior segment of the left lower lobe.

It was decided that pleuropneumonectomy was indicated and this was performed in March 1956. Examination of the resected specimen showed that there was an empyema pocket approximately 2 cm. in diameter in communication with the amputated superior segment bronchus. This was positive on both smear and culture. After operation the patient developed a high temperature. Culture of the pleural fluid revealed both tubercle bacilli and streptococci. Aspiration and administration of antibiotics failed to control this adequately. Ten days after operation he began to cough up a small amount of bloody sputum and then developed a frank bronchopleural fistula. The empyema was drained, but the patient's elevated temperature continued. The same organisms were obtained from the pericardial fluid in this man, but we were unable to aspirate any considerable amount of pericardial exudate. He finally died 6 weeks after operation. Autopsy showed that the primary cause of death was probably a purulent pericarditis. There was no residual tuberculosis in the remaining lung.

This patient had been asymptomatic for 5 years after drainage of a bronchopleural fistula and empyema, but had persistent positive gastric cultures. Bronchogram showed a persistent small empyema cavity with communication to a bron-



FIG. 7



FIG. 8

chus. This condition was treated by pleuropneumonectomy, which was complicated by fulminating mixed infection. This infection led to his death.

Figures 1 to 8 have been chosen from the cases reported upon. These show varying amounts of contrast medium having escaped into the air space. The roentgenograms were taken in different projects to best illustrate the presence of the dye. A tomogram is shown revealing a connecting bronchus.

SUMMARY

The persistent asymptomatic air space after partial pulmonary resection is associated with communicating bronchopleural fistula. The investigation of these persistent spaces by bronchography is advisable. Although the space may disappear from view in the conventional roentgenogram, the fistula can, in some cases, be still demonstrated by bronchography, and occasionally, by tomography.

The pockets may sometimes harbor tubercle bacilli and may account for persistence or extension of tuberculosis.

Six cases with asymptomatic residual air spaces following partial pulmonary resection are presented. Bronchograms or tomograms demonstrating the space and its communication with a bronchus are shown. Two of these cases had small empyema pockets of several years' dura-

tion, and the pockets accounted for a persistently positive sputum.

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BUCCOGINGIVAL CARCINOMA OF SNUFF DIPPERS

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During the past two years in the Surgery Tumor Clinic of the University of Arkansas Medical Center a number of patients were seen with carcinoma of the buccal and gingival mucosa. One feature common to many of these patients was a long history of snuff dipping. To explore this further the pathology reports and subsequently the charts for all intraoral lesions were examined for the past 10 years. From these records were gathered a group of patients who both used snuff and had intraoral malignancies. When limited to the buccal and gingival mucosa 25 such cases were found. Other oral lesions such as those of the tongue, lip, palate, oropharynx, and others are not included here. Also excluded were those cases in which the tobacco and snuff dipping history was not clear.

There have been a number of etiologic agents related to certain intraoral malignancies. Various authors^{2, 4, 6, 10, 18} have implicated chronic irritation, infection, dietary deficiencies (*e.g.*, vitamins), poor dental hygiene, as well as specific irritants such as tobacco, betel nut and buyo leaf. In only a few reports did we find snuff suggested^{1, 14} as a specific etiologic agent in intraoral malignancy.

Numerous reports from India^{7, 11, 16} stress that the incidence of carcinoma increases markedly when tobacco is included in the betel nut quid along with lime and buyo leaf. It is interesting to note that in New Britain and New Guinea,³ where the natives chew betel nut without tobacco, the incidence of carcinoma is relatively low. It has also been suggested that along with the betel nut habit vitamin deficiencies are often present.^{12, 17} These same reports stress the relationship between hypovitaminosis A and keratosis of the oral mucosa. The incidence of intraoral carcinoma in patients with the betel nut habit is approximately the same in men and women. On the other hand, the over-all statistics

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of incidence of oral cancer in the United States shows a marked preponderance of men (9:1)^{19, 21} and grade 2 and grade 3 malignancies. By contrast, the material below showed women with tumors of grade 1 malignancy.

MATERIAL

Twenty-five cases at the University of Arkansas Medical Center during the 10-year period from 1950 to 1959, inclusive, fitted the above-mentioned criteria: all patients had the snuff habit and had histologic confirmation of

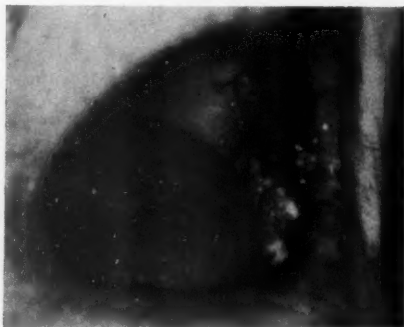


FIG. 1. D. V., 78-year-old white woman. Typical buccogingival carcinoma.

malignancy. Eleven cases were of buccal origin, 10 gingival, and 4 involved both areas so extensively that the primary site could not be defined. All 25 were women; 23 were white, and 2 colored. This is rather remarkable in that approximately equal numbers of white and colored patients, male and female, are seen in this clinic. The average age when first seen here was 67.5 years; the youngest was 44, and the oldest, 84. In each case a long history of snuff dipping was noted. The shortest exposure to snuff was 20 years, although numerous patients gave histories of dipping for more than 50 years. Most patients stated they placed the snuff in contact with the buccogingival mucosal surface for long periods each day. The lesions found corresponded to this site. Occasionally the snuff

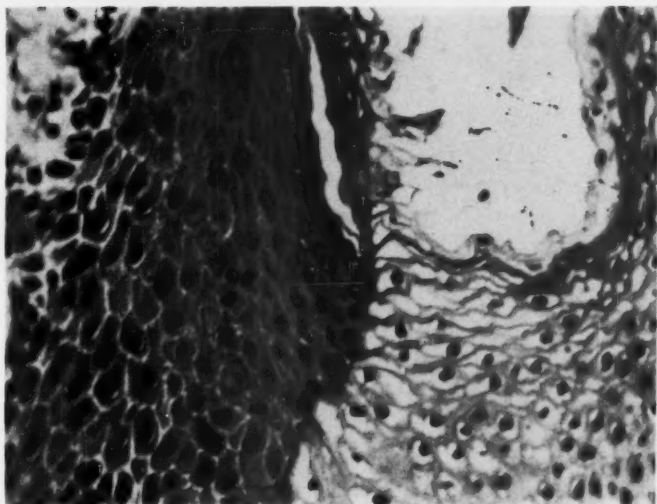


FIG. 2. L. H., 84-year-old white woman. Leukoplakia with marked accentuation of granular cell layer, hyperkeratosis. 150 X.

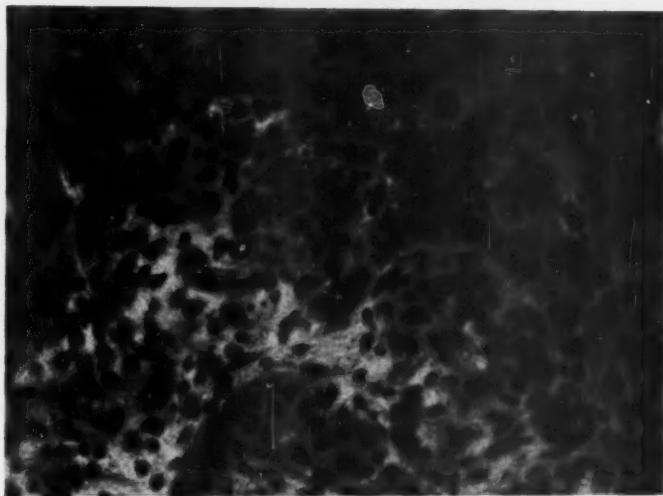


FIG. 3. E. P., 84-year-old white woman. Leukoplakic area. Tendency for leukocytes to extend into pseudoeitheliomatous portions. Pleomorphism, atypia, mitotic figures present. 300 X.

was kept on the side opposite the lesion, but when questioned many patients admitted that they had in recent times changed the location of the bolus.

Leukoplakia was a concomitant lesion and had been present for many years. Certain of these patients were followed over long periods with repeated biopsies. These showed an evolution from leukoplakia to pseudoeitheliomatous

hyperplasia to early squamous cell carcinoma. Poor dental hygiene was the rule. The majority of the patients had worn dentures for years. A few had their teeth pulled shortly before the lesion was discovered. Serologic tests for syphilis were drawn in over half of these patients; none was positive.

Typical buccogingival carcinomas were superficial, warty and extensive, measuring 2 or more

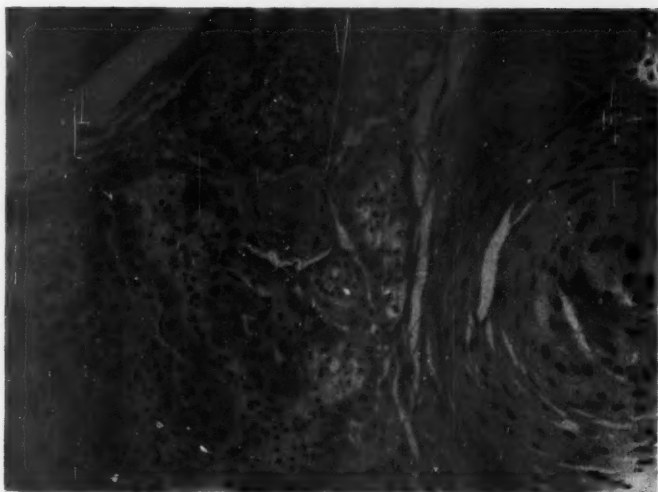


FIG. 4. L. H., 84-year-old white woman. Well differentiated squamous cell carcinoma. Pearl formation. 300 \times .

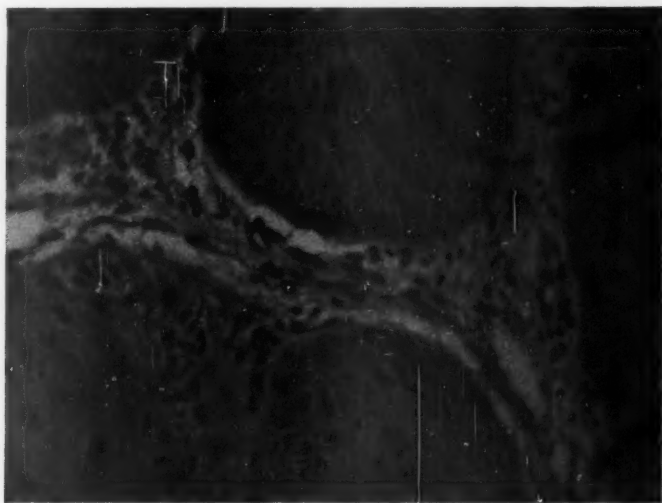


FIG. 5. E. H., 58-year-old white woman. Intact basal layer in pseudoepitheliomatous portions. Dissolution of basal cells, dyskeratosis in lower half. 300 \times .

centimeters in the smaller axis. However, even in the largest of lesions when metastases were present they were limited to the upper neck. The relative infrequency of metastases is in sharp contrast to the frequent and extensive involvement of cervical nodes in such lesions as carcinoma of the tongue. A number of patients were irradiated with generally poor results.

Similar experience was reported when this treatment was used for "betal nut" carcinoma.¹³

PATHOLOGY

Sections from the above material were reviewed. The lesion was usually a well differentiated squamous cell carcinoma. In some instances it was necessary to take numerous

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FIG. 6. E. P., 84-year-old white woman. Well differentiated squamous cell carcinoma. Pearl formation. 300 X.

sections to distinguish between pseudoepitheliomatous hyperplasia and outright malignancy. When neck dissections were performed, very few of the nodes were found to be involved, and in each case the metastatic tumor was as well differentiated as the primary. A dissolution of the basal cell layer at the site of invasion and pearl formation served as the best criteria to distinguish between the benign and malignant portions. The inflammatory reaction in the stroma was often marked. The infiltrate showed little tendency to extend into the advancing nests of carcinoma. However, in the pseudoepitheliomatous portions leukocytes were demonstrated within the acanthotic pegs. This is strikingly similar to the situation that prevails in the case of keratoacanthoma *versus* early squamous cell carcinoma of the skin. In the former an inflammatory infiltrate often extends into the lowest portions of the epithelium. In foci where the pseudoepitheliomatous hyperplasia showed pleomorphism and mitotic figures it was extremely difficult to distinguish between the two. Tumor was occasionally found in peri-

neural lymphatics, but no frank vascular invasion was noted. Leukoplakic lesions from other parts of the mouth often showed atypia.

DISCUSSION

In humans as well as in experimental animals cancers induced by chemical substances generally require a long exposure. These long exposures have been noted in cases of scrotal cancer among mule spinners,⁹ wax pressmen⁵ and chimney sweeps,¹⁵ the latter first mentioned by Sir Percivall Pott in 1775. Several reports of bladder carcinoma reveal a similarly long exposure to β -naphthylamine among dye workers.²⁰ The latent time for snuff dippers and betel nut chewers to develop their malignancies suggests such a mechanism. The exact chemical nature of the offending material in snuff and tobacco has not been clearly defined. Certainly this study would imply a carcinogenic substance is present which induces malignancy after a long period of exposure.

Last, the histologic study of this material shows how difficult it is at times to differentiate

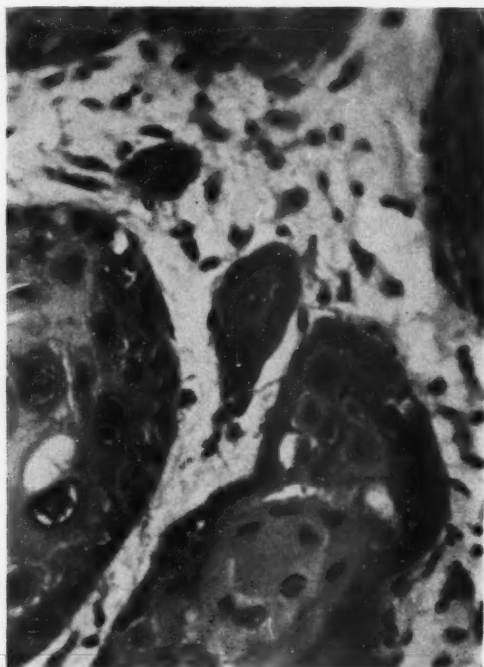


FIG. 7. E. H., 58-year-old white woman. Well differentiated carcinoma extending into underlying soft tissues. 300 X.

markedly atypical pseudoepitheliomatous hyperplasia from malignancy. King and colleagues,⁸ have made use of a fluorescein-conjugated globulin to distinguish between the above 2 conditions. Application of this technique should help resolve the problem.

SUMMARY

1. Carcinoma of the buccal and gingival mucosa was found in a number of chronic snuff dippers.

2. These patients were all elderly females, predominantly white.

3. These lesions were low grade and frequently difficult to diagnose.

4. When metastases were present they were limited to upper cervical lymph nodes.

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CARCINOID TUMORS OF THE GASTROINTESTINAL TRACT¹

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At the Veterans Administration Hospital, Hines, Illinois, there were 44 cases of carcinoid tumors of the gastrointestinal tract during the period from 1936 to 1958. All cases were in men from 27 to 73 years of age. A statistical review of these cases reveals, in some respects, a discrepancy with previously published reports^{8, 10, 16, 21} as to location and incidence of malignancy. In our series, rectal carcinoids comprised the majority of cases as compared with the appendix in other reports. The relatively low incidence of appendiceal carcinoids in our series could be explained by the fact that elderly men are less prone to appendiceal carcinoids than younger ones.^{3, 10} Of greater significance is our finding that 43.2 per cent of our carcinoids were malignant to the extent of having regional or distant metastases. An additional 15.9 per cent with no metastases showed local malignant activity, as indicated by the pathologist's report of increased mitotic activity accompanied by musculoserosal invasion. Thus, close to 60 per cent of the carcinoids reported here have shown either definite local malignant invasiveness or metastatic phenomena (table 1). At other sites of the gastrointestinal tract the malignant behavior of these tumors surpassed even that of the carcinomas, notably in the colon, where of the 6 cases of the cecum to the sigmoid there were no survivals beyond 1 year. The increased realization of the malignant activity of these tumors, plus their ability, when metastases are present, to produce high levels of serotoninemia and its accompanying systemic manifestations,

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has brought about renewed interest in carcinoids. Vigorous pursuit of serotonin physiology and its clearer understanding are gaining new impetus.

HISTORY

Oberndorfer¹⁹ in 1907 introduced the term carcinoid (*Karziinoide*) and emphasized its benign behavior. Others, using silver impregnation techniques, were able to demonstrate their origin as the argentaffin Kultschitsky cells in the crypts of Lieberkühn. In the light of present knowledge, it is significant that some of these early investigators¹² regarded them as being of endocrine origin because of their resemblance to chromaffin tissue of the paraganglia. Reports were published from time to time attesting to the ability of these tumors to metastasize. From 1952 to 1954, important contributions were made by two groups; namely, Biörck and co-workers,¹ in Sweden, and Isler and Hedinger,¹⁴ in Switzerland, which resulted in the present concept of the carcinoid syndrome. This was correlated with the work of Lembeck,¹⁵ in England, who was able to extract serotonin from a benign carcinoid tumor; Erspamer,⁹ in Italy, obtained the same substance from the intestinal tract of animals and called it enteramine. Thus, for the first time, an association between serotonin and carcinoid tumors was established.

SEROTONIN AND CARCINOID SYNDROME

In the latter part of the 19th century, observations were recorded of a vasoconstrictor substance found in clotted blood. In 1948, this substance, 5-hydroxytryptamine, was isolated by Rapport and co-workers²² and named serotonin. Serotonin is widely present throughout the body. The highest concentrations are in the argentaffin cells of the gastrointestinal tract, but it is also found in relatively large amounts in platelets and those parts of the central nervous system which are associated with autonomic nervous function. It has a generalized systemic effect producing symptoms and signs which

TABLE 1

Distribution of the carcinoid tumors in the gastrointestinal tract and their respective pathologic activity and mortality

Organ	Non-invasive	Invasive		Distal Organ Metastases	Total	Death Due to Carcinoid
		Muscle layer	Lymph nodes			
Stomach	1	0	1	0	2	0
Duodenum	2	0	0	4	6	3
Jejunum	1	0	1	0	2	0
Ileum	4	5	1	0	10	0
Meckel's	2	0	0	0	2	0
Cecum	0	0	0	4	4	4
Colon	0	0	0	2	2	2
Appendix	1	2	1	0	4	0
Rectum	7	0	2	3	12	3
Totals	18	7	6	13	44	12
Percentage	40.9	15.9	13.6	29.6	100	27.3

have been attributed to its excessive secretion by carcinoid tumors and their metastases.

The following are the manifestations which are now referred to as the carcinoid syndrome: recurrent, intermittent, cyanotic flushing accompanied by fluctuation of the blood pressure; tachycardia; diarrhea; asthma and hyperpnea; telangiectasia; and frequently, signs of pulmonic stenosis with right heart failure. Autopsies of these cases show right sided endocardial fibrosis with valvulitis, resulting in pulmonary stenosis and tricuspid insufficiency. None of these pathologic findings has been found on the left side of the heart except in the presence of left-to-right shunts. It has been established that the lungs are rich in monoamine oxidase, an enzyme capable of detoxifying serotonin (5-hydroxytryptamine) to 5-hydroxyindolacetic acid (5-HIAA), an inactive product found in the urine of these patients. It has been determined that the indole compound serotonin is derived from the amino acid tryptophane.²⁵ The various steps, enzymes, and tissues participating in this process are illustrated in figure 1. The occasional finding of pellagra in patients with the syndrome is explained by two mechanisms: the disturbance of tryptophane metabolism, which interferes with niacin synthesis; and disturbed intestinal function with diarrhea, resulting in decreased absorption from the intestines.

A number of patients have been observed to

have temporary mental disturbances with this syndrome, but the connection of serotonin with chronic mental disorders such as schizophrenia remains unsubstantiated. In the pharmacologic studies of serotonin antagonists, including dibenamine, lysergic acid, diethylamide, ergotamine, and some of the sympatholytic agents, trial treatments with chlorpromazine were conducted most frequently. To date, no success clinically or significant depression of the urinary excretion of 5-HIAA have been noted.^{2, 24}

Not all patients, even those with extensive metastases, exhibit the features of the syndrome. On the other hand, two recently published cases^{24, 30} of primary ovarian carcinoid without metastases (arising from the gastrointestinal component of ovarian teratomas) did exhibit the syndrome. A few cases of metastasizing bronchial carcinoids have been recently reported with hyperserotonemia and the accompanying carcinoid syndrome.^{7, 27} Whether or not these are primary bronchial tumors is open to debate.

Pressure and massage of the primary tumor with the resultant liberation of serotonin may produce palpitation, tachycardia and flushing.^{5, 24} Undue excitement and ingestion of alcohol may have similar effects.^{2, 24} Ingestion of large amounts of certain food substances such as cheeses, which are rich in serotonin and its precursors, may also precipitate the attack. Bananas, which are also rich in serotonin, if consumed in sufficient quantity will yield abnormally high blood serotonin and 5-HIAA urinary levels in normal subjects. Because of the deleterious effects of high serotonin levels, it is desirable to remove as much of the serotonin producing tumor as possible, even to resections of liver metastases.³³ To date, only about 70 cases of confirmed carcinoid syndrome have been reported.

PATHOLOGY

Carcinoids are typically small, firm, and well circumscribed neoplasms which are yellow in color and contain fat cells. Later, they may extend from their submucosal position into all layers of the gut. Direct extension into the adjacent mesenteries forms fibrous tissue exceeding several times the size of the primary tumor. This will frequently result in bowel adhesions—which are the most common cause of small intestine obstruction due to carcinoids in

METABOLISM OF TRYPTOPHANE

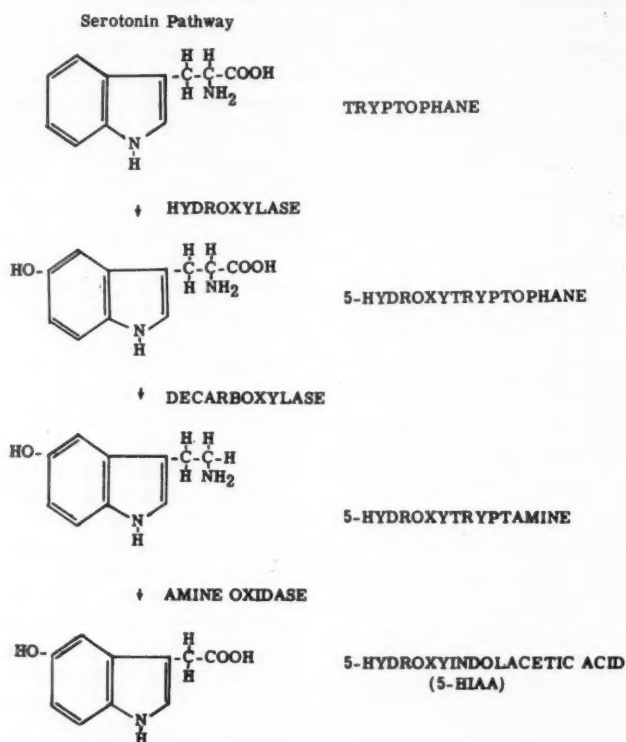


FIG. 1

other series.^{10, 16} In the appendix, the tumor in about 90 per cent of the cases is found at or near the tip^{21, 23} and is often mistaken for fecolith. Extra-appendiceal carcinoids frequently project into the lumen as sessile or polypoid nodules, single or multiple. Histologically, they are comprised of islets of epithelial cells which are small, polygonal or round, with a small number of mitotic figures present and surrounded by a bed of fibrous stroma. The nuclei are round, oval, or basophilic, surrounded by acidophilic cytoplasm containing granules which take on a characteristic argentaffin positive stain when treated with ammoniacal silver nitrate solution. Some carcinoids, notably those in the rectum, do not possess the argentaffin staining quality.²³

The usual criteria for tumor malignancy, such as mitosis and cell anaplasia, are not entirely applicable to carcinoids, and this has been well emphasized previously by others.^{9, 10, 16} Because

of this, gross and microscopic invasiveness of underlying muscle layers and serosa remains the means for determination of local malignant activity. Of the 44 cases, 19 (43.1 per cent) were noninvasive and had no evidence of metastases at operation or on later follow-up; of the 25 cases with invasiveness of muscle wall, 17 (68.0 per cent) had lymph node involvement and an additional 13 (52.0 per cent) had distant metastases. Thus, contrary to the opinion of some, local invasiveness has been a reliable criterion for malignancy in this series.

DISTRIBUTION

Carcinoids may be found in any age, ranging from 10 days to 89 years.²³ The average age of extra-appendiceal carcinoids is between 55 and 60,²² whereas the appendiceal carcinoids are found in the 30's. The multiplicity of carcinoids has been stressed by some and reported in as

high as one-third of the cases.^{10, 21} This was seen in 5 (11.6 per cent) of 44 of our cases. Table 1 shows the distribution and pathologic classification in this series.

The incidence of carcinoids is placed between 0.1 to 0.5 per cent of all tumors.²¹ According to Dockerty,⁶ from the pathologist's standpoint, 90 per cent of carcinoids are found in the appendix and the remaining 10 per cent elsewhere. This, essentially, is the reverse in our series. For a comparison of the data of this series with that of the series collected by Diffenbaugh and Anderson,⁸ see table 2.

SIGNS, SYMPTOMS AND TREATMENT

None of the cases in this report was diagnosed preoperatively. Of the 28 cases coming to surgery because of symptoms attributed to the tumor, 23 had pain, 4 had painless melena as their initial symptom, and 3 had jaundice. The signs and symptoms were distributed according to the location of the involved organ. Duodenal tumors gave rise to epigastric pain, whereas small and large bowel tumors were lower abdominal and diffuse in character; appendiceal carcinoids brought on signs and symptoms of appendicitis. Large rectal carcinoids were accompanied by tenesmus, and low back pain with rectal bleeding in one instance. Of the smaller rectal carcinoids 2 had painless bleeding. In the 3 cases of jaundice, a tumor was located at the ampulla of Vater. Roentgenographic signs of distal small bowel kinking should be suggestive of carcinoid in that region. Miller and Herrmann¹⁷ in 1942 described this sign, peculiar to these carcinoids, as an acute buckling of the bowel due to serosal invasion. Treatment consists of adequate enterectomy of the involved small intestine and its mesentery. Appendiceal carcinoids are adequately treated by appendectomy and resection of the mesoappendix. When situated at the base of the appendix, a right hemicolectomy is indicated because recurrence is more likely. In the rectal carcinoids there is direct correlation between size and malignancy. In these, it would therefore be indicated to perform a more radical abdominoperineal excision for lesions larger than 2 cm. which show evidence of infiltration and ulceration. Local excision should be reserved for those rectal carcinoids which are less than 2 cm. in diameter and show no evidence of local invasion or lymph node extension.^{10, 18} This

TABLE 2

Comparison of 44 cases of this series with 1496 cases collected by Diffenbaugh and Anderson as to their distribution and pathologic activity

Location	Series Collected by Diffenbaugh and Anderson			This Series		
	Total	Metastases	per cent	Total	Metastases	Per cent
Stomach.....	29	4	13.7	2	1	50.0
Gallbladder....	4	0	0			
Duodenum.....	21	4	19.0	6	4	66.6
Small bowel...	438	150	34.2	12	2	16.6
Appendix.....	825	29	3.5	4	1	25.0
Meckel's diverticulum..	8	0	0	2	0	0
Cecal area.....	34	27	79.1	4	4	100.0
Colon.....	7	3	42.8	2	2	100.0
Rectum.....	130	18	13.8	12	5	41.6
Total.....	1496	235	15.7	44	19	43.2

point is illustrated by the case of a 57-year-old white man with a history of rectal bleeding of 1 year's duration who was found to have a 3.5 cm. rectal carcinoid which was locally excised on the presumption of histologic benignity of the lesion. The patient returned 2 years later with inguinal node metastases, proved by biopsy, and expired due to liver and lung metastases. In 130 cases of reported rectal⁸ carcinoids, regardless of size, 13.8 per cent had malignant potentiality which with time became disseminated. Rectal carcinoids which were small and localized were found in an average age of 47 as compared with 56 years of age for those which had widespread dissemination. The prophylactic value of routine proctoscopic examinations cannot be overemphasized in the tumors which were incidentally discovered in this group.

DISCUSSION

Carcinoid tumors are no longer to be thought of as quaint neoplasms which occasionally metastasize and have a uniformly prolonged course. The variation in the incidence of malignancy in the different regions of the gastrointestinal tract is probably on the basis of variation in time elapsed before detection is accomplished. Thus, carcinoids of the appendix

are most frequently removed for symptoms of appendicitis secondary to fibrotic obliteration of the lumen and are seen in an earlier age than in other regions. Similarly, the rectal cases which were detected on routine proctoscopy were smaller, noninvasive, and occurred in an age group a decade younger than those which were larger and had become symptomatic. The submucosal position of carcinoids and their relatively small size tend to make bleeding or early obstruction less likely in the larger intestinal lumina such as the colon and cecum. Melena occurred in 2 of our 6 cases of the large bowel carcinoids above the rectum, and one in the terminal ileum. Rectal carcinoids, on the other hand, will bleed, even when small and not invasive, due to erosion of the mucosa probably secondary to stercoral trauma. This was seen in 3 of our 12 rectal carcinoids, only 1 of them being invasive and larger than 1 cm.

SUMMARY

1. Forty-four cases of carcinoid are presented, with appendiceal carcinoid markedly less common than generally believed.

2. Based on local invasiveness and distal spread, there was an incidence of malignant activity in 59.1 per cent of the cases.

3. The relation of serotonin to the carcinoid syndrome is presented.

4. A review of the pathology, clinical features, and management of carcinoid is given.

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THE USE OF THE BIPOLAR MYOCARDIAL ELECTRODE IN THE SURGICAL TREATMENT OF COMPLETE HEART BLOCK

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The patient with complete heart block and associated Stokes-Adams syncope is a serious problem in medical management. The variable clinical course with its often sudden catastrophic events can be a complete and fearsome disability to the patient who is prone to sudden death. Since uniform results by pharmacologic means for treatment have not been achieved, this paper will describe the use of the bipolar myocardial electrode in the surgical treatment of certain cases of refractory and crippling heart block.

Complete heart block is defined as a complete atrioventricular dissociation. In this instance, the ventricular rate is slower than the atrial (generally under 50 with the exception in congenital heart block or in digitalis intoxication where the ventricular rate may be 75 or more on occasion).⁶ At the present time heart block can be classified into two groups: (1) acquired and (2) traumatic. In a series of 278 cases studied by Rowe and White in 1958, the etiologic factors for group 1 were as follows: coronary heart disease alone, 35 per cent; coronary heart disease with acute infarction, 14 per cent; coronary heart disease and hypertension, 24 per cent; rheumatic heart disease, 8 per cent; digitalis intoxication, 6 per cent; congenital, 6 per cent; miscellaneous (amyloid, diphtheria, and so forth) 4 per cent, and unknown 3 per cent.⁶ The advent of intracardiac surgery has created the second grouping—here a precipitous and often persistent occurrence of the phenomenon, constituting an important source of morbidity and mortality in these surgical patients. Although statistics are as yet incomplete, Kirklin has experienced this complication in 5 per cent of interventricular septal repairs during or after surgery.

As stressed by Penton and co-workers,⁵ the clinical course of patients with complete heart block is very variable. Of these patients 38 per

cent experience Stokes-Adams attacks—exhibiting an abrupt loss of consciousness with or without convulsions secondary to transient ventricular asystole.⁶ The figures on survival rate in heart block show variance in several series. Penton⁵ states that the average duration of life after the first appearance of complete heart block is 26 months. Wood⁹ prognosticates that in acquired cases life expectancy averages $4\frac{1}{2}$ years. Rowe and White⁶ relate a survival time of 18 months in coronary heart disease, 9 months in coronary heart disease with acute infarction, 47 months in coronary heart disease with hypertension, 79 months in rheumatic heart disease and 31 months in the entire series. In congenital heart block, however, the clinical course is characterized by a long survival time and relative freedom from symptoms. Surprisingly in the series of Rowe the patients with concomitant syncope live twice as long as those without. This favorable association is most striking in the group with accompanying angina pectoris or previous myocardial infarction (table 1).

Medical therapy is administered to prevent or relieve asystole, or to increase the idioventricular rate to a level where symptoms disappear. The sympathomimetic amines (epinephrine, ephedrine, or Isuprel) are most commonly employed. The list of other drugs prescribed includes atropine, thyroid extract, barium chloride, belladonna, molar sodium lactate, and even steroids.

The forerunner of the modern surgical approach to the refractory case of complete heart block was G. Aldini,¹ who in 1802 was the first to apply an electrode to the heart—the subject being a decapitated criminal, dead for 2 hours. In 1954, Zoll and his co-workers⁹ described an external pacemaker designed to tide the heart over a critical period by stimulating rhythmic contractions of the heart. This instrument, because of its size and the relatively large voltages required, presents many inherent difficulties in

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long term management. Being dependent upon a power source, its usefulness is limited to the length of the electric cord. The associated muscular contractions produce pain which frequently requires profound sedation. Where more than transient use is required, ulceration with chronic secondary infection at the point of electrode contacts will occur.

Lillehei and his group,⁷ cognizant of the shortcomings of the external pacemaker and aware of complete heart block as constituting an important source of mortality in intracardiac surgery, developed a transistorized pacemaker with wire implantation into the myocardium. Where a mortality of 100 per cent in untreated cases following operative heart block had been reduced to 40 per cent with the use of Isuprel, the use of a myocardial electrode at the time of cardiac surgery in a recent series of 55 cases has resulted in no mortality. In these cases stimulation had been maintained until the return of adequate rhythm, and then the wire electrode had been easily withdrawn.

Dr. Seymour Furman² of New York City has described the use of an intracardiac pacemaker in which an electrode catheter is passed by vein into the right ventricle and connected to an external pacemaker. In one of the two reported cases, this catheter enabled a patient with complete heart block to undergo radical surgery, maintaining throughout a normal cardiac rate and rhythm. The catheter was promptly withdrawn postoperatively. In the second case the catheter was electively inserted in an elderly patient with critical heart block and left in place for 13 weeks and 5 days with spontaneous resumption of ventricular impulses on removal. William Glenn³ of Yale has also described in a case the stimulation of the heart by a myocardial wire connected to a buried subcutaneous coil receiver which responded to radio frequency waves transmitted from a remote source. This functioned well for 21 days with the return of syncopal attacks and ultimate death on the 41st postoperative day.

Dr. Samuel Hunter of St. Paul, Minnesota, and Mr. Norman Roth⁴ of Medtronic, Inc., Minneapolis, Minnesota, have recently explored the use of a bipolar myocardial electrode for the pertinent need in acquired cases of complete heart block with marked disability. In their method two stainless steel electrodes are im-

TABLE 1
Effect of Stokes-Adams on survival times (38% of series)

Disease	Months with	Months without
Coronary heart disease	75	18
Coronary heart disease with infarction	45	9
Coronary and hypertensive disease ..	63	47
Rheumatic heart disease	96	79
Entire series	72	31

bedded in a 1.5 by 2.5-cm. silastic silicone patch. An insulated coaxial wire conducts the current to the electrode through the chest wall from a Medtronic transistor pacemaker. This pacemaker is small, measuring 2.5 by 5 by 10 cm. and weighing 10 oz., contains an easily replaceable mercury battery with 300 hours' capacity, generates 7.5 volts, and is easily strapped to the chest. The silicone patch is imbedded in and sutured to the myocardium of the right ventricle, and the coaxial cable brought out through the chest wall. This can be done either through a classical cardiomyotomy incision or through an anterior thoracotomy incision. This method eliminates skeletal muscle irritation, skin ulceration, and patient immobility (fig. 1).

Twenty-five cases have been reported by Dr. Hunter with 3 postoperative deaths; one from coronary infarction, one from myocarditis secondary to infection, and one from failure of the pacemaker. The remainder are doing well.

Therefore, we wish to present our experiences with 2 cases of heart block accompanied by Stokes-Adams syndrome, using the bipolar electrode and transistor pacemaker.

CASE REPORTS

Case 1. In January 1958, a 49-year-old white male rancher was first seen with progressively frequent and incapacitating Stokes-Adams syncope following a myocardial infarction in September 1957. There had been no response to the usual therapeutic regime, and the patient was virtually bedridden. On September 4, 1958, under an intercostal block of xylocaine, an anterior pericardiectomy was performed with implantation of a stainless steel braided wire insulated with polyethylene tubing into the right ventricular myocardium. For 5 subsequent months, the patient was completely asymptomatic, at full

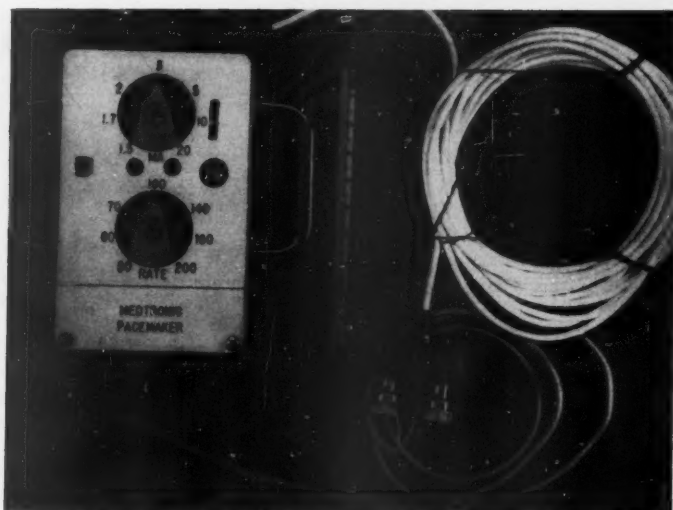


FIG. 1. The Medtronic pacemaker with bipolar electrode

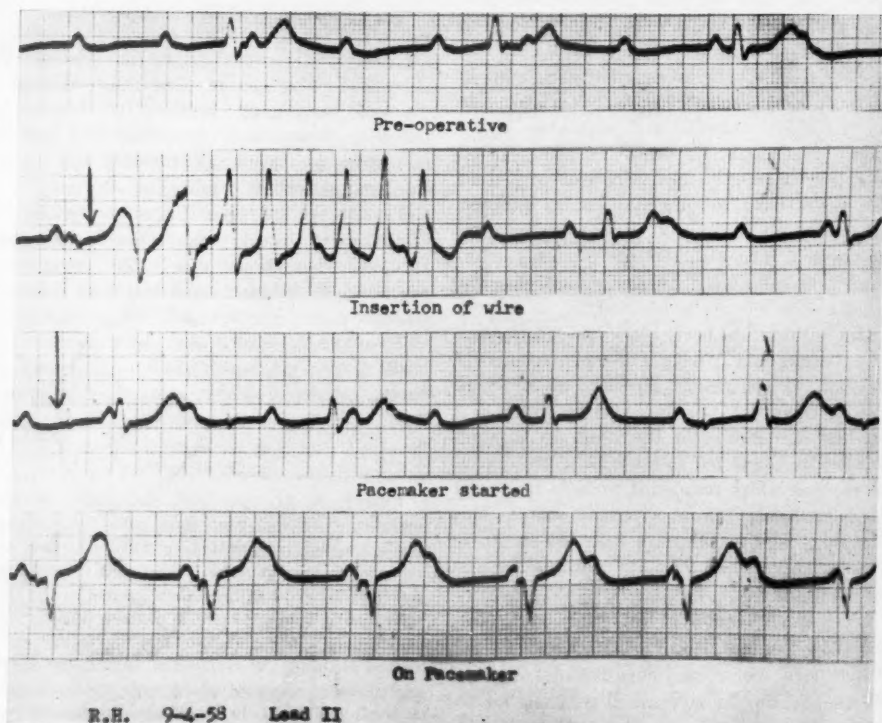


FIG. 2. Electrocardiograms of case 1 taken before, during and after attachment of the pacemaker

employment, and enjoying golf. Thereafter, cardiac function was such that a replacement of the myocardial wire was deemed necessary, and this was done on June 25, 1959, through the old operative scar with only a 4-day hospitalization. The pacemaker again worked satisfactorily but for a much shorter time—4 weeks. Knowing the experimental success of the bipolar electrode, a third operation was carried out on August 16, 1959. This electrode has continued to work satisfactorily, but only with the addition of booster stimulation increasing the output of the pacemaker on 2 occasions. Therefore, he has had satisfactory pacemaking for 12 of the past 17 months (fig. 2).

Case 2. The second patient was a 74-year-old white woman who had had an established diagnosis of heart block since 1953. Because of the increasing severity of the Stokes-Adams syndrome during the past year, she had been hospitalized for 3 months with no response to the usual medicines. On August 16, 1959, a bipolar electrode was inserted under a local intercostal and infiltrative anesthesia through an anterior cardiectomy incision. Her postoperative course was marked by complete amelioration of all symptoms and by the ability to ambulate and travel without incident. In the latter part of December 1959, an abscess developed about the entrance site of the coaxial cable that did not respond to antibiotics or to drainage. Because of an advancing chest wall cellulitis, a second operation was performed on January 25, 1960, with first the insertion of a new bipolar electrode through a low left anterolateral thoracotomy incision onto a fresh area of myocardium and then the removal of the old electrode through the old anterior incision. There was subsequently complete healing of the primary infected site. At the present time the patient is well with no syncope and with a pulse of 80. Thus, she has had 7 months of uninterrupted satisfactory pacemaking without recurrence of symptoms.

SUMMARY

Two cases of complete heart block treated by surgery (bipolar myocardial electrode and transistorized pacemaker) are described in the foregoing presentation. One case has had effective pacemaking for 12 out of 17 months; the

other, for 7 consecutive months. The method is considered as an effective but not ideal method in giving relief to the critically ill patient suffering with complete heart block.

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ADDENDUM

The bipolar myocardial electrode has since ceased to function in both patients. In case 1 the plate was removed on December 22, 1960, because of inactivity and infection. In spite of booster stimulation the plate ceased to function in case 2 on April 15, 1960. Both patients have refused re-insertion. Both cases are alive with persistent heart block.

RESECTION AND REPLACEMENT OF SEGMENTS OF THE COMMON AND INTERNAL CAROTID ARTERIES WITH A TEFLON GRAFT UTILIZING A SHUNT PROCEDURE

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The eminent neurosurgeon Walter E. Dandy¹ long ago pointed out that ligation of the internal or common carotid artery is followed by a high mortality rate and a high percentage of cerebral complications. Following this procedure the cerebral complications may be delayed, and include hemiplegia, aphasia, mental changes or epilepsy. Ligation of the common carotid artery causes death and disability from (1) cerebral anemia from inadequate collateral circulation through the circle of Willis, or (2) cerebral thrombosis and embolism, which occur abruptly 12 hours to several days postoperatively.

The early history of wounds of the common carotid artery, as well as of those incurred in World War I and World War II, reveal that ligation for control of hemorrhage frequently met with death or severe cerebral complications. In 1552, Ambroise Paré attended a patient who had been wounded in a duel, as reported by Watson and Silverstone.² An épée wound across the neck had caused severe laceration of the common carotid artery of the left side. It is reported that Doctor Paré arrested the profuse hemorrhage and spared the patient's life, but the patient developed a left monoplegia and aphasia. During World War I the United States Army Medical Department reported only 25 carotid artery wounds.³ The mortality rate of this group was recorded as 44 per cent but no other particulars were given. In World War II, teams of the Second Auxiliary Surgical group reported 17 cases of wounds of the common carotid artery.³ Of these, the artery was ligated in 12, and 8 survived; of the 8 surviving cases, 2 had transient hemiplegia. Of the 5 not ligated, 4 died. The over-all mortality rate was 47 per cent.

Aneurysm of the common carotid artery is a

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relatively uncommon lesion. Reid's review of these aneurysms at the Johns Hopkins Hospital included only 10 cases.⁶ Between 1927 and 1947, only 5 cases were reported from the surgical service of the University of Pennsylvania. Aneurysms of the common carotid artery may be lumatic, but are more commonly arteriosclerotic in origin. Aneurysm of the internal carotid artery, particularly of the intracranial portion, is a relatively common condition.

Until the development of shunt mechanisms for grafting, 6 types of management had been recommended for carotid aneurysm, as follows: (1) none, (2) proximal ligation of the common carotid artery, (3) distal ligation of the common or external or internal carotid arteries, (4) proximal and distal ligation simultaneously or in stages, (5) aneurysmorrhaphy, or (6) excision following proximal and distal ligation.

SHUNT GRAFTS

The specific problem during resection of lesions in the innominate and common or internal carotid arteries is to maintain adequate blood supply to the brain at all times.

In 1954, Mahorner and Spencer⁴ described the use of shunt grafts to maintain circulation through a vessel while a lesion in that vessel was being excised. It was their opinion that a shunt technique would have greatest use during replacement of segments in the upper thoracic aorta and aortic arch. Since their article was published, the various methods for extracorporeal circulation have simplified the insertion of grafts into the thoracic aorta.

In 1958, Soltero and Greenberg⁵ reported the experimental use of a shunt consisting of two lucite cannulas with Tygon connecting tubing to bypass lesions during resection of arteries.

The surgical indications for resection of portions of the common and internal carotid arteries are encountered in the following situations: (1)

the treatment of carotid aneurysms or arteriovenous fistulas, (2) repair of these vessels following trauma, (3) excision of carotid body tumors, (4) neck dissection for metastatic carcinoma, and (5) occlusive vascular disease.

It seems logical that the high mortality rate of carotid artery resection might be reduced by a quick, simple, and efficient method for shunting blood above the site of pathology into the extracranial portion of the internal carotid artery.

REPORT OF CASE

F. W. F., a 45-year-old man, was admitted to St. Francis Hospital, Wichita, Kansas, June 11, 1959, with a chief complaint of a pulsating mass in the left midcervical region since June 1958.

Physical examination revealed a pulsating mass at the level of the carotid bifurcation. This mass measured about 2 by 2½ cm. It extended under the edge of the sternocleidomastoid muscle. The blood pressure was 120/78 in the left arm, and 160/80 in the right arm. Routine examinations of the blood and urine were normal. Roentgenograms of the chest were normal.

Operation was performed on July 12, 1959. Under endotracheal anesthesia, the cervical portion of the common and internal carotid arteries was completely exposed. An arteriogram was performed which corroborated the clinical diagnosis of an extracranial carotid artery aneurysm (fig. 1). There was no evidence of

intracranial pathology. The operative procedure consisted of placing a shunt above and below the aneurysm, utilizing a 5/16 Teflon graft with 12-gauge needles tied to either end (fig. 2), which were inserted into the arteries to maintain a constant flow of blood into the cerebrum (fig. 3). After insertion of the shunt the superior thyroid and external carotid arteries were ligated. The aneurysm, which involved the carotid bulb and



FIG. 1. Extracranial carotid artery aneurysm.

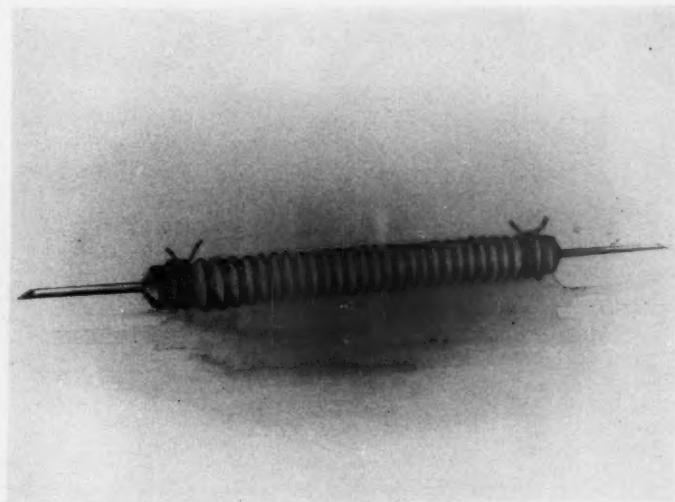


FIG. 2. Teflon prosthesis with 12-gauge needles attached

about 3 cm. of the proximal internal carotid artery, was then resected with a segment of normal artery. A second Teflon graft was then anastomosed into the intervening defect and an end-

to-end anastomosis with 5-0 silk was accomplished in the usual manner (fig. 4). After insertion of this graft the shunt was removed: Rather brisk bleeding was encountered at a point where the needles

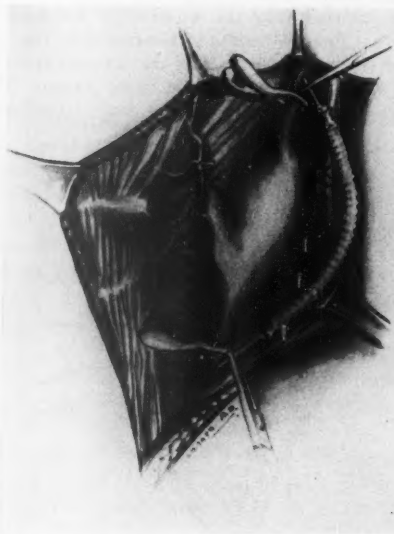


FIG. 3

FIG. 3. Shunt bypassing blood flow above and below point of pathology

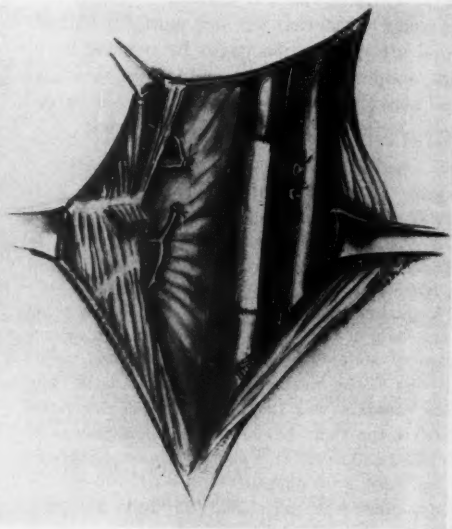


FIG. 4

FIG. 4. Teflon prosthesis anastomosed to common and internal carotid artery

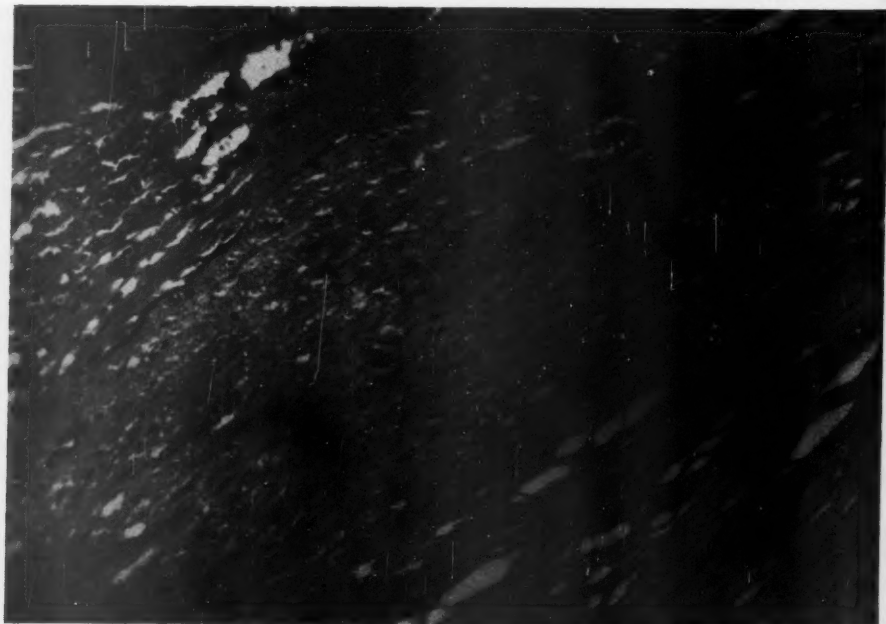


FIG. 5. Intimal and medial degeneration with lipid deposits

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had been inserted and these openings were repaired with a simple purse-string suture. We have learned that this can be obviated by placing a purse-string suture into the wall of the artery before inserting the needles and then closing this purse-string on withdrawal of the 12-gauge needles.

The wound was closed in the usual manner and immediately after operation normal pulses were palpable in the carotid areas. The postoperative course was smooth and uneventful and at no time was there evidence of neurologic disturbances. The pathologic report revealed a left internal carotid aneurysm and the histologic report revealed advanced arteriosclerosis of the involved internal carotid artery (fig. 5).

On August 24, 1959, the patient was readmitted to the hospital for carotid arteriography, which demonstrated that the graft and the left internal carotid artery were patent and of normal caliber. The external carotid was not visualized as it had been previously ligated. The patient was dismissed the following day.

SUMMARY

The severe neurologic manifestations and mortality after interruption of carotid artery circulation can be prevented by the use of a simple shunting procedure that protects the cerebrum during the operation.

A case of successful resection of an arteriosclerotic aneurysm involving a segment of the common carotid and a segment of the internal carotid has been described. The preparation of a simple Teflon shunt has been outlined.

Acknowledgment. I am indebted to Doctor Nouvarat Cen Sarn, surgical resident at St. Francis Hospital, for the original drawings.

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PERPHENAZINE AS A PROPHYLACTIC ANTIEMETIC IN SURGERY*

A DOUBLE-BLIND STUDY AMONG 580 PATIENTS

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The most common postoperative problems are pain and vomiting. Postoperative emesis is undesirable, and even dangerous, because it may increase wound pain, disturb fluid and electrolyte balance by causing dehydration, disrupt the wound, delay alimentation and, in rare instances, cause aspiration pneumonia.

Postoperative emesis usually is attributed to analgesic or anesthetic agents, or to complications of surgery. Smessaert¹⁷ studied the records of 2000 surgical patients at the New York Hospital in an attempt to isolate the factors which influence postoperative vomiting. The general incidence was 24.3 per cent. The incidence was significantly higher in females than in males, and higher in young people than in those who were middle-aged or old. There was no significant correlation with body type.

The type of anesthetic was found to be significant; for example, among general anesthetics cyclopropane and/or ether is twice as likely to provoke postoperative emesis as thiopental sodium and/or nitrous oxide. However, the duration of anesthesia did not seem to be significant unless it was very prolonged (4 or more hours). The type of operation appears to be of some significance although it was not possible to establish a positive statistical correlation. The incidence of vomiting seemed to be greatest among patients who had undergone surgery on the gastrointestinal tract.

Wang and colleagues²⁰ demonstrated the existence of a true vomiting center deep in the medulla and of a superficial chemoceptive emetic trigger zone which regulates the activity of circulating emetic factors, including certain

anesthetic and analgesic agents used in surgery. Wang¹⁹ suggests that phenothiazines exert their antiemetic effect by competing with the triggering agents and thus blocking their action at the chemoceptive emetic trigger zone.

The marked antiemetic potency of perphenazine (Trilafon), a ring-substituted phenothiazine, was first observed by Rosenkilde and Govier¹⁵ in their animal studies. The drug afforded significant protection against apomorphine-induced emesis in dogs. On a milligram-for-milligram basis, the antiemetic activity of perphenazine was several times greater than that of other phenothiazines in current use.¹⁴

This study, testing perphenazine as the prophylactic antiemetic agent, was undertaken because all effective antiemetics which had been used previously had serious and sometimes uncontrollable side effects, especially when administered immediately after surgery. Significant variations in pulse, respiration, and blood pressure attributable to these agents were fairly frequent, as was potentiation of surgical anesthesia sufficient to put patients back to sleep in the recovery room. Also, use of some of these drugs is contraindicated in certain age groups. In a small and busy recovery room, these disadvantages assume serious proportions. A rapidly effective antiemetic for intravenous administration, with minimal side effects, was required. We especially wished to avoid, if possible, an increase in postoperative drowsiness which would significantly prolong time in the recovery room.

Perphenazine was tested with the double-blind method among a continuous series of 580 surgical patients. A 5-mg. dose of perphenazine or an indistinguishable placebo was administered by the continuous intravenous drip method immediately after operation. Relevant clinical variables and postoperative results were recorded before the code was broken. It was found that 287 patients had received the perphenazine and 293 had received the inert material. The recorded

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* This study was performed at the Tucson Medical Center. The perphenazine (Trilafon) was provided through the courtesy of J. Black, M.D., of the Division of Clinical Research, Schering Corporation, Bloomfield, New Jersey.

† Diplomate of the American Board of Anesthesiology.

variables were then separated into the experimental and control series and analyzed.

The following information was obtained for all patients: sex and age; type of anesthesia; type of surgery; effect of medication on pulse, respiration and blood pressure; time in the recovery room; effect of medication on recovery; effect of medication on the postoperative narcotics requirement; effect of medication on the incidence of nausea and/or vomiting. Nausea, as well as vomiting, was recorded in this series because nonproductive retching also threatens the integrity of the surgical wound and adds appreciably to the patient's postoperative discomfort. As Cummins³ states, "... nausea represents the conscious awareness of impulses exciting the vomiting center, though at times only subliminally."

The age distribution and the ratio of males to females were similar in both groups, although there were slightly more females and fewer persons 19 years or under in the perphenazine-treated group (table 1). Since the incidence of postoperative vomiting has been shown to be higher in females and higher among young persons, these slight differences between the control and experimental series would cancel out.

The standard types of preoperative medication were used in all patients and there were no significant differences between the experimental and control groups. The types of anesthesia were similar in both groups; in neither group was there a greater number of patients who had received an anesthetic agent especially likely to provoke emesis (table 2). All patients had some type of general anesthesia except 44 in the con-

TABLE 2

Types of Anesthesia	Placebo: 293 Pa- tients	Perphen- azine: 287 Pa- tients
Thiopental sodium (Pentothal) or methitural sodium (Neraval)	6	7
Thiopental or methitural with cyclopropane or halothane (Fluothane). . . .	31	33
Thiopental or methitural with cyclopropane or halothane and succinylcholine chloride (Anectine)	92	84
Thiopental or methitural with succinylcholine	37	26
Thiopental or methitural with nitrous oxide or ethyl ether	18	20
Thiopental or methitural with nitrous oxide or ethyl ether and succinylcholine	49	49
Thiopental or methitural with cyclopropane or halothane and nitrous oxide or ethyl ether	2	4
Thiopental or methitural with cyclopropane or halothane and nitrous oxide or ethyl ether plus succinylcholine	6	9
Tetracaine hydrochloride (Pontocaine)	33	31
Tetracaine with thiopental*	4	2
Tetracaine with thiopental and cyclopropane	1	1
Tetracaine with thiopental and nitrous oxide		2
Tetracaine with thiopental and cyclopropane plus succinylcholine		1
Tetracaine with thiopental and pentobarbital sodium (Nembutal)†		1
Lidocaine hydrochloride (Xylocaine)	11	11
Lidocaine with thiopental	3	3
Lidocaine with thiopental and cyclopropane		2
Lidocaine with thiopental and nitrous oxide		1

* Thiopental was administered only in quantity sufficient to induce sleep.

† Pentobarbital was administered only in quantity sufficient to induce sleep.

trol group and 42 in the treated group who received only spinal or caudal agents. All patients who received spinal anesthesia also were given oxygen to assist respiration. The other patients who received tetracaine or lidocaine for primary anesthesia also received some type of supple-

TABLE 1

Sex and age of 580 surgical patients

	Placebo: 293 Patients		Perphenazine: 287 Patients	
	No.	Per Cent	No.	Per Cent
Males	113	38.57	92	32.06
Females	180	61.43	195	67.94
14-19 ys.	13	4.45	5	1.74
20-45 ys.	156	53.43	163	56.80
46-59 ys.	73	25.00	76	26.48
60 ys. and older	50	17.12	43	14.98
Not recorded	1			

TABLE 3

Types of Surgery	Placebo: 293 Pa- tients	Perphen- azine: 287 Pa- tients
Thyroidectomy	0	1
Tonsillectomy	1	2
Bronchoscopy	27	12
Laryngoscopy; tracheoscopy; esophagoscopy	4	3
Gastroscopy	1	0
Appendectomy	5	3
Cholecystectomy	2	5
Colostomy	1	0
Nephrectomy; nephrolithotomy	1	1
Resection of colon	0	1
Laparotomy, diagnostic	1	1
Hysterectomy	11	9
Other gynecologic surgery <i>via</i> lapa- rotomy	5	15
Dilation and curettage	62	51
Minor vaginal surgery; vaginal ex- amination	3	6
Biopsy or removal of cyst from breast	10	11
Herniorrhaphy	14	7
Transurethral resection	8	3
Excision of bladder tumor	5	0
Miscellaneous minor genitourinary surgery	1	5
Cystoscopy	38	52
Hemorrhoidectomy	10	16
Miscellaneous minor rectal surgery	3	5
Excision of cyst from extremity	5	11
Orthopedic surgery	44	38
Plastic surgery	17	16
Vascular surgery	7	6
Insertion of radium	0	2
Oral surgery	7	5

mentary anesthesia, usually thiopental, because they did not wish to be awake during surgery. Minimal amounts of thiopental or pentobarbital, only enough to provoke light hypnosis, were used in these cases.

The types of surgery also were randomized. In neither group was there a greater number of patients who had undergone surgery, such as gastrointestinal, which is considered to be more likely to provoke postoperative emesis (table 3).

Since the factors which are likely to influence the incidence of postoperative emesis were randomly and almost equally distributed between the control and experimental series of patients,

any difference in results could be attributed to the presence or absence of the experimental agent.

Perphenazine did not affect the pulse or respiration as recorded in the recovery room. Significant increases or decreases (more than 30 points in the pulse rate; more than 33 per cent of the respiration rate) occurred in approximately the same percentage of patients in both the treated and control groups (table 4).

A slight tendency toward depression of the blood pressure, as recorded in the recovery room, was observed among the group of patients who had received perphenazine (table 5). There was significant depression (systolic blood pressure depressed more than 20 points and/or diastolic blood pressure depressed more than 10 points) among 18.4 per cent of patients in the control group and among 33.4 per cent of patients in the treated group. Elevations of the blood pressure, to the same extent, were recorded in 7.5 per cent of the control series and 6 per cent of the experimental series.

Administration of perphenazine did not significantly affect the time in the recovery room (table 6). Excluding the 7 patients in each category who remained longer than 4 hours, it was found that the mean average time in the recovery room was 80 minutes for the control series and 85 minutes for the treated series.

Perphenazine very slightly increased the tendency to drowsiness during response or

TABLE 4

Effect of Medication on Pulse and Respiration*	Placebo: 293 Patients		Perphenazine: 287 Patients	
	No.	Per Cent	No.	Per Cent
Pulse increased more than 30 points	1	0.34	1	0.35
Pulse decreased more than 30 points	4	1.37	7	2.44
Pulse not significantly af- fected	288	98.29	279	97.21
Respiration increased more than 33%	7	2.39	9	3.14
Respiration decreased more than 33%	12	4.10	11	3.83
Respiration not signifi- cantly affected	274	93.51	267	93.03

* Recorded in recovery room after injection.

awakening of patients in the recovery room (table 7). In the group which received the placebo, 96 patients (33 per cent) were more than normally drowsy, and in the treated group 119 patients (41 per cent) were more than normally drowsy.

Perphenazine apparently has a slight tendency to reduce the postoperative narcotics requirement (table 8). In the control series, 5 patients (1.7 per cent) and in the perphenazine-treated series 10 patients (3.5 per cent) required less than the usual (15 mg.) amount of meperidine.

The incidence of postoperative nausea and/or vomiting was reduced by the prophylactic administration of 5 mg. of perphenazine. Symptoms occurred in 42 (14.3 per cent) of the patients who had not received the drug, and in 27 (9.4 per cent) of those who had received it (table 9). Only one of the patients who vomited, in both series, was under 19 years of age. This was a female of 17 years who had received perphenazine.

Previous studies of perphenazine as a prophylactic antiemetic also yielded good results according to reports by Albert and colleagues,¹ Cutolo and Kleppel,⁴ Moore and colleagues,¹⁰ Musetto

TABLE 6

Time in Recovery Room	Placebo: 293 Patients	Perphenazine: 287 Patients
Less than 15 min.	0	1
16-30 min.	13	15
31-45 min.	28	30
46-60 min.	74	60
61-75 min.	64	62
76-90 min.	35	33
91-105 min.	20	19
106-120 min.	20	16
121-135 min.	5	9
136-150 min.	10	10
151-165 min.	5	7
166-180 min.	4	10
181-195 min.	2	1
196-210 min.	1	3
211-225 min.	2	3
226-240 min.	1	0
Over 4 hr.	7	7
Not recorded	2	1

TABLE 7

Effect of Medication on Recovery*	Placebo: 293 Patients		Perphenazine: 287 Patients	
	No.	Per Cent	No.	Per Cent
Awake.....	78	26.62	63	21.95
Awake but drowsy.....	13	4.44	26	9.06
Awake after responding normally.....	3	1.02	12	4.18
Awake after responding drowsily.....	9	3.07	8	2.79
Responding well.....	32	10.92	33	11.50
Responding well after responding drowsily.....	7	2.39	5	1.74
Responding normally.....	81	27.65	58	20.21
Responding drowsily.....	67	22.87	80	27.87
Not recorded.....	3	1.02	2	0.70

* Recorded in recovery room.

and colleagues,¹¹ Phillips and colleagues,¹² and Scurr and Robbie¹⁶ in general surgery; by Harley and Mishler⁷ and by Nielsen¹² in ocular surgery; by Cannistra and Abrams² and by Gready and colleagues⁶ in obstetrics; by Krasner⁸ in oral surgery; and by Stewart¹⁸ in urologic surgery.

These investigators commented on the absence of untoward reactions from perphenazine. There was little or no hypotension following administration, probably because the adrenergic-

TABLE 5

Effect of Medication on Blood Pressure*	Placebo: 293 Patients		Perphenazine: 287 Patients	
	No.	Per Cent	No.	Per Cent
Significant elevation				
Systolic more than 20 points.....	6	2.05	2	0.70
Diastolic more than 10 points.....	13	4.44	9	3.14
Systolic plus diastolic more than 20/10 mm. Hg.....	3	1.02	6	2.09
Total.....	22	7.51	17	5.93
Significant depression				
Systolic more than 20 points.....	8	2.73	8	2.79
Diastolic more than 10 points.....	35	11.95	49	17.07
Systolic plus diastolic more than 20/10 mm. Hg.....	11	3.75	39	13.59
Total.....	54	18.43	96	33.45
Significantly unaffected...	217	74.06	174	60.62

* Recorded in recovery room after injection.

TABLE 8

Postoperative Narcotics Requirement*	Placebo: 293 Patients		Perphenazine: 287 Patients	
	No.	Per Cent	No.	Per Cent
No narcotic required or given.....	241	82.24	230	80.14
Usual† amount of narcotic required.....	34	11.60	36	12.54
Less than usual amount of narcotic required....	5	1.71	10	3.49
More than usual amount of narcotic required....	5	1.71	3	1.05
Discomfort or pain, but no narcotic given.....	4	1.37	4	1.39
Narcotic given before experimental drug.....	4	1.37	4	1.39

* Recorded in recovery room.

† Meperidine (Demerol), 15 mg. intravenously.

blocking effect of perphenazine is not marked. Slight drowsiness, which may slightly prolong recovery time, has been reported by a few investigators but was not considered serious.

Although Mathewson⁸ states that most phenothiazines have an "appreciable" potentiating effect on narcotics, the experience of Albert, Gready, Krasner, and Nielsen and their groups^{1, 6, 8, 12} with perphenazine indicates that little or no narcotic potentiation is produced by the usual (5 mg.) doses of this drug. Gready and colleagues⁶ found that potentiation occurred only when 10 mg. or more of perphenazine were administered; at this level the dosage of meperidine could be lowered. Cannistra and Abrams² gave 15 mg. of perphenazine, in 3 divided doses, with scopolamine and a barbiturate to their obstetric patients. At this dosage level, the potentiating effect of perphenazine on the scopolamine was sufficient to make administration of meperidine unnecessary. Apparently if narcotic potentiation by perphenazine is desired, 10 mg. or more should be administered.

Careful studies of the cardiovascular, respiratory and central nervous systems were made by Albert and his group¹ after intravenous administration of 5 mg. of perphenazine. No untoward effects were observed. When used as premedication for surgical anesthesia, perphenazine produced desirable relaxation and slight drowsiness, and served as a powerful antiemetic and mild

soporific during the immediate postoperative period.

Cutolo and Kleppel⁴ administered perphenazine before or after surgery and in general found little difference in results. Postoperative administration seemed more likely to cause drowsiness, but these authors considered this effect desirable in postoperative patients. Surgical patients were relaxed and comfortable during the postoperative period; there was no depression of vital signs; fluids were tolerated earlier. Perphenazine was also useful therapeutically to reduce the intensity and duration of emesis in postoperative patients who had not received a prophylactic dose of the drug. Relief usually occurred within 30 minutes after administration whereas in untreated patients symptoms persisted for several hours.

We compared our results with those of previous investigators (table 10). The incidence of postoperative emesis among surgical patients, without perphenazine, ranged between 8 and 54 per cent with the average being 22 per cent. Among similar patients treated with perphenazine, usually 5 mg. parenterally immediately before or after surgery, the incidence of emesis ranged between 3 and 25 per cent, with the average being 6 per cent. Our results fall within the ranges reported by other investigators.

The rather wide range of reported incidences, with and without perphenazine, is probably attributable to differences in grading criteria used by the various investigators. Some recorded both nausea and vomiting; others recorded vomiting only. However, since the same criteria were used by each investigator for both the control and experimental series, the general results are roughly parallel: perphenazine reduced by two-thirds the incidence of postoperative nausea and/or vomiting.

TABLE 9

Effect of Medication on Emesis*	Placebo: 293 Patients		Perphenazine: 287 Patients	
	No.	Per Cent	No.	Per Cent
Nausea and/or vomiting..	42	14.33	27	9.41
Nausea and/or vomiting before injection only....	7	2.39	11	3.83
No nausea or vomiting....	244	83.28	249	86.76

* Recorded in recovery room.

TABLE 10

Summary of reported experience with perphenazine to prevent postoperative emesis

Investigators	Control Groups			Perphenazine Groups			
	No. of patients	Nausea and/or vomiting		No. of patients	Dosage	Nausea and/or vomiting	
		No.	Per Cent			No.	Per Cent
Albert and colleagues ¹	300	24	8.00	300	5 mg. i.v.*	10	3.00
Cutolo and Kleppel ⁴	46	25	54.34	62	5 mg. i.m.*	7	11.29
Gready and colleagues ⁶	300	42	14.00	700	5-25 mg. i.m.	27	3.85
Harley and Mishler ⁷	25	4	16.00	25	4 mg. i.v.	0	—
Moore and colleagues ¹⁰	306	55	17.97	304	3.75 mg. i.v.	19	6.25
Musetto and colleagues ¹¹	No control group			102	5 mg. i.m.	10	9.80
Phillips and colleagues ¹³	102	49	48.04	99	4 mg. i.m. repeated once	25	25.25
Scurr and Robbie ¹⁶	100	21	21.00	100	5 mg. i.m.	7	7.00
Smessaert ¹⁷	2000	486	24.30	No perphenazine-treated group			
Summary of published reports	3179	706	22.20	1692	Usually 5 mg. parenterally	105	6.20
This study	293	42	14.33	287	5 mg. i.v.	27	9.41

* i.v., intravenously; i.m., intramuscularly.

† The criterion in this study was severe nausea and/or vomiting.

We continue to use perphenazine in the recovery room. Occasionally the prophylactic dose of 5 mg. is repeated; this, of course, could not be done in the controlled study. This practice has considerably increased the usefulness of the drug and at present the incidence of postoperative emesis among our surgical patients is approximately 4 per cent. When the dosage is increased, there is a slight increase in postoperative drowsiness but not to an extent which significantly prolongs time in the recovery room.

Perphenazine fulfills all of the requirements which we consider essential for postoperative antiemesis. It helps produce the "ideal" postoperative state described by Dobkin⁵ in which ataraxia and antiemesis persists during the several hours until the acute disturbances caused by anesthesia and surgical trauma have subsided.

SUMMARY

Perphenazine, 5 mg., or an inert placebo was administered by the intravenous drip method to a continuous series of 580 surgical patients immediately after operation. Records were kept of the age and sex of each patient, of the types and amounts of preoperative medication and anesthesia, of the surgical procedures, of varia-

tions in pulse, respiration and blood pressure, of the time and response in the recovery room, of the postoperative narcotics requirement, and of the incidence of postoperative nausea and/or vomiting. After these data had been recorded, the double-blind code was broken. Perphenazine had been given to 287 patients and 293 had received the placebo. Differences between the treated and control groups were then analyzed.

Clinical variables (age, sex, preoperative medication and anesthesia, and type of surgery) were random and almost equal for the two groups and therefore could not have influenced the results, which were as follows:

1. Perphenazine exhibited a slight tendency to depress the blood pressure but the drug did not affect pulse or respiration.

2. There was a slight, but not significant, increase in postoperative drowsiness in the group of patients who had received perphenazine. Time in the recovery room did not vary significantly between the two groups.

3. There was a slight decrease in the postoperative narcotics requirement in the group of patients who had received perphenazine.

4. Postoperative prophylactic administration of 5 mg. of perphenazine reduced the incidence of emesis following surgery. Nausea and/or vomit-

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ing occurred in 27 (9.41 per cent) of the 287 patients who had received perphenazine, and in 42 (14.33 per cent) of the 293 patients who had not received the drug.

5. Perphenazine is still used in the recovery room. Occasionally the prophylactic dose of 5 mg. is repeated. This has further reduced the incidence of postoperative emesis so that at present it is approximately 4 per cent.

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RESULTS OF ANTERIOR EXCISION OF RUPTURED CERVICAL DISCS

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In 1959 Drs. Hall, Fralick and I,¹ presented a preliminary report of our first year's experience with anterior excision of ruptured cervical intervertebral discs and interbody fusion before the

TABLE 1

Statistical analysis of first 100 cases
(May 14, 1958, to January 13, 1960)

Average age.....	41.86 yr.
Range of ages.....	17 to 65 yr.
Sex	
Male.....	46
Female.....	54
Cause of injury	
Rear end collisions.....	26
Automobile crashes.....	19
Fall with injury to head, neck or shoulder.....	17
Blow upon head, neck or shoulder.....	16
Freak accidents.....	17
Unknown.....	5
Disc spaces operated upon.....	168
C 3-4.....	5
C 4-5.....	38
C 5-6.....	71
C 6-7.....	46
C 7-D1.....	8
Type of bone used for fusion	
Autogenous.....	153
Bone bank.....	15
(In 2 cases, both bone bank and autogenous bone was used.)	

Southwestern Surgical Congress and later demonstrated the actual operation at St. Luke's Hospital in Denver, Colorado. We have continued this procedure throughout the past year and now have currently analyzed our first 100 cases (table 1) for simple statistical data and have evaluated our first 75 cases (table 2) for clinical results.

The operative procedure is the relatively new

Presented at the 12th Annual Meeting of the Southwestern Surgical Congress, Las Vegas, Nevada, March 30, 1960.

TABLE 2

Clinical evaluation of results in the first 75 cases* (May 14, 1958 to October 17, 1959)

Groups	Multiple	Solitary	Total	Per Cent
I. Very good—Patients at work with no significant symptoms.....	22	16	38	50.6
II. Good—Patients at work with few symptoms.....	9	4	13	17.3
III. Patients partially relieved of pain and disability but still unable to hold a steady job.....	16	7	23	30.7
A. Patients whose symptoms may indicate the need for further surgery upon one or more additional discs				
B. Patients whose surgery is too recent to show maximum improvement				
C. Patients showing improvement who will probably never be sufficiently relieved to enter upon gainful employment				
1. Paralytic, 2				
2. Emotionally disturbed, 5				
IV. Patients whose condition remained unchanged.....	0	1	1	1.4
V. Failures—Patients whose symptoms are worse, who have developed non-union with severe pain and disability or acute angulation or other mal-union with pain and disability.....	0	0	0	0
Totals.....	47	28	75	100.0

*Twenty five of the cases tabulated in Table 1 are excluded as surgery was performed after October 17, 1959.

approach to a deranged* cervical intervertebral disc, designed and performed by Cloward.² We are now convinced that this procedure is safer and more effective than the posterior laminectomy that has been the procedure of choice for over 30 years. Beneficial results were apparent to us from the very beginning and statistical evaluation after 2 years' practice confirms our first impression.

As we previously stated, no patient is selected for surgical treatment who has not had at least 3 months of conservative treatment without significant improvement with the exception of those with fracture dislocations of the cervical spine and those with acute solitary unilateral disc ruptures with pain and disability corresponding to solitary nerve root involvement.

Any case selected for surgery must have one or more pathologically deranged discs demonstrated by discogram, and during the course of the discography, symptoms must be reproduced in their original pattern.

The cases (table 2) in groups I and II have had excellent results. In these groups we have a total of 51 cases or 68 per cent. Groups III and IV comprise 24 cases or 32 per cent. However, of the 24 patients in the groups III and IV, there are 8 patients who will probably never be gainfully employed because of paralysis or severe emotional disturbance. Therefore, in this series there is the possibility of only 67 patients ever again being gainfully employed. By this operative procedure 51 or 76.1 per cent of these 67 patients have been returned to employment.

A report of particular significance to us is that

* Types of derangement found in cases evaluated at this time comprise disc rupture, disc derangement, disc derangement with osteophytes in the nerve foraminae or spinal canal, "arthritis," acute subluxation and fracture-dislocation.

of Drs. Braaf and Rosner³ because it provides a basis for contrasting the results of anterior and posterior operation upon deranged cervical discs. They say, "Cervical laminectomy was performed in ten cases, with five obtaining excellent results and the other five either receiving no material relief of symptoms or developing annoying complications following surgery, manifested by weakness and vasomotor changes in the hands and occasional selected atrophy of the muscles of the upper extremities."

We conclude that the 10 cases of Drs. Braaf and Rosner operated by posterior laminectomy showed excellent results in 5, or in 50 per cent. Our current statistics reveal that anterior excision in 67 cases has produced excellent results in 51 cases, or in 76.1 per cent. Furthermore, our experience has demonstrated that continuing improvement can be expected within the remaining 16 cases. This potential improvement should be reflected by a greater percentage of excellence in later evaluations.

In summary, this report, coupled with our original preliminary report, reveals statistically that major beneficial results can be obtained in the treatment of symptomatic deranged cervical intervertebral discs by the method of anterior surgical excision of the disc and interbody fusion, as described by Cloward.²

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Editorial

THE "BENIGN" GASTRIC ULCER

Almost every physician in the United States agrees that duodenal ulcer is preferably treated conservatively and not by resection, in contradistinction to the consensus of those in many other countries, such as Brazil, that all duodenal ulcers should be resected. Advocates of surgical treatment contend that results of medical treatment are not good because it is impossible for patients to adhere to a medical regimen. In this country operation is considered only in the presence of surgical complications, such as perforation, hemorrhage or obstruction, or in the rare patient whose symptoms cannot be controlled by a conservative regimen. If these criteria are adhered to, probably less than one-half of 1 per cent of all persons with duodenal ulcer will require operation.

In contrast to the almost complete unanimity in this country concerning the advisability of conservative treatment of duodenal ulcer, considerable controversy exists about the best treatment for gastric ulcer. Although at one time I believed that gastric and duodenal ulcers were similar, I am now convinced that treatment of gastric ulcers must be considered in an entirely different light from that of duodenal ulcer. It is my firm conviction that with the possible exception of the very superficial gastric ulcer these lesions should be resected. Moreover, I believe that the physician who treats a gastric ulcer conservatively assumes a responsibility that is seldom justified.

The current consensus among pathologists is that benign gastric ulcers seldom, if ever, become malignant. This is in direct contrast to the concept held 25 years ago that chronic gastric ulcers frequently undergo malignant change. Although it may be presumptuous for a clinician to dispute the contention of pathologists, it is my belief that chronic gastric ulcers can undergo malignant change. Segi and Kurihara¹ reported a yearly increase in the incidence of gastric cancer, and they attributed this to the high incidence of gastric ulcer, which they believed undergoes malignant change. It does not require much imagination to envision that persistence of an ulcer in a highly susceptible epithelial surface,

such as gastric mucosa, might produce cancer. It is well known that such changes occur in the skin in the form of a Marjolin ulcer, and there is every reason to believe that this can occur in the stomach as well.

An additional reason why I believe that gastric ulcer does undergo malignant change, is that the stomach is one of the two organs in the body where the incidence of cancer is decreasing in the United States at a time when the incidence in all other organs is increasing. The incidence of cancer of the uterine cervix is decreasing, probably because women are extremely cognizant of the danger of cancer and consult their physicians regularly, so that precancerous cervical lesions are detected and treated before a malignant lesion develops. Similarly, more patients with gastric ulcer are being treated by gastrectomy, and I believe that by removal of the ulcer the premalignant lesion is eliminated and consequently the incidence of gastric cancer is reduced.

It is particularly desirable to prevent cancer in the stomach because of the almost uniformly bad results obtained in the treatment of clinically diagnosable gastric cancer. The 5-year survival rates in such cases range from 5 to 12 per cent, whereas in ulcerative lesions of the stomach in which it is impossible to determine before microscopic examination whether the condition is malignant, the 5-year survival rate is infinitely better. Brown and co-workers² reported that in 106 ulcerative lesions of the stomach thought to be benign but proved to be malignant, among those operated on early the 5-year survival rate was 75 per cent. In our own series this rate is 80 per cent.

Another reason why gastric ulcers should be resected is the impossibility of determining preoperatively whether an ulcerating lesion in the stomach is benign or malignant. It is impossible for the radiologist to exclude the possibility of a malignant lesion. It is equally impossible for the gastroscopist, the surgeon, at laparotomy when he is able to palpate the lesion, and even the pathologist, when he has the specimen in his hand, to say unequivocally that the lesion is not malignant. Indeed, at times it may be difficult

to make a diagnosis of cancer unless serial sections of the ulcer are made. This fact is illustrated by the experience at the Tulane University School of Medicine. For 20 years the members of the Department of Pathology had used a microscopic section illustrating a benign gastric ulcer. After such long usage many of the slides were broken, and it was decided to cut more sections from the same block. Much to the consternation of the staff, carcinoma was found in the new slides!

Because of the uniformly poor results obtained in the treatment of clinically diagnosable cancer of the stomach, and because no better results can be obtained by more radical dissection, such as total gastrectomy, it is our conviction that if the salvage rate is to be increased, resection must be performed before cancer can be diagnosed. If one delays until the lesion is clinically cancer, it is too late!

Another reason for advocating resection of gastric ulcer is the fact that the conservative treatment of this lesion, in contradistinction to the conservative treatment of duodenal ulcer, is not satisfactory. Moreover, the complications of gastric ulcer are frequently much more serious than similar complications of duodenal ulcer. In a series of 303 patients with gastric ulcer Palmer³ found that 138 (45.5 per cent) had complications; 102 of these (33 per cent) had gross hemor-

rhage, of which 26 (8.5 per cent) required emergency operations to control the bleeding, and an additional 13 (4 per cent) required operation either to control hemorrhage or perforation.

Whereas a short course of conservative therapy under strict hospital control may not be too hazardous in the treatment of gastric ulcer, one must not be lulled into a false sense of security if the ulcer heals, since in the presence of gastric acidity a malignant lesion can ulcerate because of peptic digestion. In such instances therapy that would tend to control the hyperacidity can permit healing of the ulcer even though malignant. The hazard of delay is shown by Brown and associates' experience.² Although their 5-year survival rate in ulcers thought to be benign but found to be malignant and treated early by resection was 75 per cent, the rate dropped to 54 per cent when resection was delayed.

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Book Reviews

The editors of *THE AMERICAN SURGEON* will at all times welcome new books in the field of surgery and will acknowledge their receipt in these pages. The editors do not, however, agree to review all books that have been submitted without solicitation.

Importance of the Vitreous Body in Retina Surgery. Edited by CHARLES L. SCHEPENS, M.D., Director of the Retina Foundation, Boston, Mass. 235 pp. The C. V. Mosby Company, St. Louis, 1960.

This is a record of the Second Conference of the Retina Foundation held on May 30 and 31, 1958. The contributors include Balazs, Custodis, Hruby, Okamura, Pischel, Schepens, D. Shafer, T. Smith, Straatsma, and Zimmerman. The first part of the book deals with the microscopic examination of the vitreoretinal junction, and the physiology of the vitreous. Clinical examination of the vitreous by indirect ophthalmoscopy and by slit lamp examination is then discussed. The latter part of the book deals with the various surgical methods devised for repairing retinal detachments.

The contributors do not hesitate to discuss differences of opinion, and this adds to the value of the book. For example, massive vitreous retraction is defined differently by three investigators.

This is an important book and will be of value to all physicians interested in the problems of retina surgery.

R. D. RICHARDS, M.D.

Surgery of Repair as Applied to Hand Injuries. By B. K. RANK, C.M.G., M.S., F.R.C.S., F.R.A.C.S., AND A. R. WAKEFIELD, M.S., F.R.C.S., F.R.A.C.S. 288 pp., The Williams & Wilkins Company, Baltimore, 1960.

This text was obviously not written for the surgeon who has had little experience in dealing with hand injuries. It is rather a book which assumes that the reader has had moderate experience in the field and presents an interesting philosophy on the over-all care of hand injuries. Actually the basis of the text is a 10-year cumulative experience with all types of hand injuries compiled by the authors with little reference to basic operative procedures.

Included in the general descriptive section of the book are sections concerning the social significance of hand injuries, the surgical anatomy of the hand, and a detailed section on the examination and appraisal of an injured hand. The actual discussion of principles of treatment is divided

into primary, intermediate, and secondary forms of treatment for injured hands at various stages. Special emphasis is placed on the burned hand, hand injuries in children, and hand prosthesis. Throughout the book the reconstructive aspect of hand surgery is repeatedly stressed.

The book is well written and any difficulty encountered in reading it may be related to the method of presentation rather than the content. There are numerous photographs of illustrative cases; however, basic principles are rarely diagrammed or discussed. As the authors state, this is not a basic textbook of hand surgery but rather a work meant primarily for the discriminative interest of those who see and treat hand injuries.

W. F. HOLDEFER, JR., M.D.

Surgical Philosophy in Mass Casualty Management. By WARNER F. BOWERS AND CARL W. HUGHES. Charles C Thomas, Springfield, Ill., 1960.

With opinions based on rationalizations from combat surgery and analogies from recent civilian disasters, the authors present an integrated realistic plan for the management of casualties resulting from such a catastrophe.

Speaking bluntly, they point out that due to a lack of common sense understanding of the problem, most physicians function ineffectively in providing adequate medical care under such adverse conditions. Lessons learned from previous disasters show that the academic, idealistic concept of maximum medical care for all must of necessity bow to the philosophy of casualty management which affords most benefit for the greatest number of persons under the existing conditions. The authors emphasize that careful preplanning is mandatory to insure effective utilization of all medical personnel and describe in detail how to formulate a workable operational plan.

They believe that the key to ultimate success in actual management of casualties resides in proper categorization or sorting of the wounded into groups by priority for treatment. Specific criteria are established to aid the doctor in performing this most difficult task. They describe specific treatment for the various injuries which may be encountered and enumerate the surgical compromises which must often be made. An appraisal of the penalty in mortality for delays in medical care is also considered.

In this stimulating presentation, every phy-

sician will discover helpful new ideas toward the solution of the serious problem of caring for mass casualties which may arise from a community medical disaster.

WILLIAM S. KISER, M.D.

Ciba Foundation Symposium on Haemopoiesis, Cell Production and its Regulation. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., M.R.C.P., AND MAEVE O'CONNOR, B.A. 490 pp. Little, Brown and Company, Boston, 1961.

This book contains the papers and discussions of an international conference on hemopoiesis, which was held February 2 to 4, 1960, under the sponsorship of the Ciba Foundation. Professor J. M. Yoffey from the University of Bristol served as the initiator, organizer, and chairman. Twenty-seven internationally known investigators par-

ticipated. Among the subjects stressed were those relating to the nature of the hemopoietic stem cell, the role of lymphocytes in blood cell production, quantitative relationships of cell production, the kinetics of erythro- and granulocytopoiesis, and humoral influences on blood cell formation and release. The papers are illustrated well with charts, graphs and microphotographs. Complete lists of references are included after each paper. The discussions are of particular interest in that they represent an informal expression of the thoughts, plans, and problems of the group.

The subject matter is very technical, and the book will be of value mainly as a reference for hematologists and for those working in closely related areas of investigation.

C. L. SPURLING, M.D.

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